LIST OF UPDATES FOR

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, SIXTH REVISION OCTOBER 2023

(August 2023 Updates)

There is one (1) amendment for the August 2023 DRGD Updates as follows:

Main Body of DRGD Third Edition, Fifth Revision July 2023

Section B: Product Registration Process

1. Amendment of information, 10.2 Correspondence, Page 46

LIST OF UPDATES FOR

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, SIXTH REVISION OCTOBER 2023

(August 2023 Updates)

Amendment of Section B: Product Registration Process

1. Amendment of information in 10.2 Correspondence on Page 46 by –

   (a) substituting the word, “shall” with “may” in “The application shall be rejected if the applicant fails to respond to the correspondence from NPRA to submit the required clarification/ supplementary data/ information or documentation within six (6) months from the first correspondence date.”

LIST OF UPDATES FOR
DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, SIXTH REVISION OCTOBER 2023
(September 2023 Updates)

There are six (6) amendments for the September 2023 DRGD Updates as follows:

Main Body of DRGD Third Edition, Fifth Revision July 2023

Section B: Product Registration Process

1. Addition of information, 6.3.3 Registration of For Export Only (FEO) Product, Page 27
2. Amendment of information, 7.14 *Halal* Logo, Page 42

Appendix of DRGD Third Edition, Fifth Revision July 2023

Appendix 19: General Labelling Requirements

3. Amendment of information, Additional Requirements in 1. Label for Immediate Container and Outer Carton, Page 4
4. Amendment of information, Additional Requirements in 1. Label for Immediate Container and Outer Carton, Page 5

Appendix 32: Explanatory Notes for Repackers

5. Amendment of information, 4. Examples of Types of Repacking Activity, Page 3
6. Addition of information, 4. Examples of Types of Repacking Activity, Page 3

LIST OF UPDATES FOR

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, SIXTH REVISION OCTOBER 2023

(September 2023 Updates)

Amendment of Section B: Product Registration Process

1. Addition of information in 6.3.3 Registration of For Export Only (FEO) Product on Page 27 by –

(a) adding the following statements:

"a) Products intended for export can be registered via two (2) pathways:
(i) Product registered for the local and export market
(ii) Product registered as For Export Only (FEO) product

c) The product registration number for FEO products is differentiated from the product registration number for products registered for the local and export market with the addition of an "E" suffix, e.g. MAL11070001AE.

j) In general, the labelling requirements for products intended for exportation shall follow the requirements imposed by the country of importation and are not subject to the labelling requirements for products registered for the Malaysian market.

- Refer to 7.14 *Halal* Logo for information on the use of *halal* logo on registered product labels for the export market."

2. Amendment of information in 7.14 *Halal* Logo on Page 42 by –

(a) deleting the following statement:

"b) The logo is **NOT** allowed to be used on the label of registered products other than the categories listed above."

(b) adding the following statements:

"e) In addition, the *halal* logo may be used voluntarily on the label of registered scheduled poison products (excluding veterinary products) that are exported to other countries for products stated in a) (i) and a) (ii) in 6.3.3 Registration of For Export Only

(FEO) Product on condition that the country of importation allows the use of *halal* logo on the product label. However, *halal* logo is **not** permitted on the label of such products marketed locally.

f) The *halal* logo issued by the following shall be accepted for products intended for exportation:

(i) JAKIM
(ii) Islamic Body recognised by JAKIM
(iii) Islamic Body certified by the country of importation.

g) The *halal* logo is **NOT** allowed to be used on the label of registered products other than the categories listed above."

Amendment of Appendix 19: General Labelling Requirements

3. Amendment of information in Additional Requirements f) in 1. Label for Immediate Container and Outer Carton on Page 4 by –

(a) substituting the following paragraph:

"f) No stick-on label is permitted. Any usage of stick-on label shall have prior approval by the Authority. The label shall be made from good quality material and not easily torn or peeled off. The Authority will only consider the following situations:

Stick-on label of such information is permitted:

Words with "Controlled Medicine", "*Ubat Terkawal*", "Keep out of reach of children" and "*Jauhkan daripada capaian kanak-kanak*", PRH information, and Malaysia Specific Labelling Requirements (if any) shall be printed in a single label."

with the following paragraph:

"f) Stick-on label refers to an additional label affixed onto an approved immediate label (D1) and/or outer carton (D2). The stick-on label shall not cover any information on the approved immediate label (D1) or outer carton (D2). The stick-on label shall be made from good quality material and not easily torn or peeled off.*

Stick-on label of the following is permitted:*

i. 'Controlled Medicine/*Ubat Terkawal*' (For scheduled poisons only), 'Keep out of reach of children', '*Jauhkan daripada capaian kanak-kanak*' (reiterations that are similar in meaning is allowed), and Product Registration Holder information. These statements shall be printed on a single label.
ii. Malaysia-specific label requirements such as name and content of preservative(s)
iii. Specific labelling requirements of a product according to Appendix 20: Specific Labelling Requirements
iv. '*Diimport/diedarkan oleh*…'
v. 'Halal logo' according to 7.14 *Halal* Logo
vi. Security label (hologram)
vii. 'Sample Not For Sale', 'Physician's sample not for sale', or 'Professional sample not for sale'
viii. Barcode (inventory management)
ix. QR Code (e-labelling/ inventory management)
x. Security seal (tamper-evident feature)
xi. Recommended Distributor's Price (RM)/ Recommended Retail Price (RM) (Optional)

** The terms above should be read in its entirety and together with Appendix 32: Explanatory Notes for Repackers to ensure full understanding and correct implementation.*

No other stick-on label is permitted. Any usage of stick-on label other than the above shall require prior approval by the Authority."

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(September 2023 Updates)

4. Amendment of information in Additional Requirements h) in 1. Label for Immediate Container and Outer Carton on Page 5 by –

(a) inserting the phrase, "/barcode" after "QR code" in "Use of QR code is permitted only for the purpose of monitoring inventory of the product, such as batch number, expiry date and manufacturing date, BUT NOT for linkage to any website."

(b) inserting the phrase, "/barcode for this purpose" after "QR code" in "The addition of QR code on registered product labels without variation approval from NPRA may be considered only if that is the only proposed change to the currently approved labels."

(c) adding the statement, "The use of a QR Code for the purpose e-labelling is permitted in accordance with the Guideline on Electronic Labelling (E-Labelling) for Pharmaceutical Products in Malaysia."

Amendment of Appendix 32: Explanatory Notes for Repackers

5. Amendment of information in 4. Examples of Types of Repacking Activity on Page 3 by –

(a) deleting the phrase, "Examples of" from the title, "Examples of Types of Repacking Activity".

(b) substituting activity no. 4, "To affix an immediate label to a container of product that contains information such as Product Name, Dosage Form, Name of Active Substance(s), Strength of Active Substance(s), Batch Number, Manufacturing Date, Expiry Date, Route of Administration, Storage Condition, etc." with "To affix an approved immediate label (D1) to a container of a product".

(c) substituting activity no. 5, "To affix label of outer carton that contains information such as Product Name, Dosage Form, Name of Active Substance(s), Strength of Active Substance(s), Batch Number, Manufacturing Date, Expiry Date, Route of Administration, Storage Condition, etc." with "To affix an approved outer carton label (D2) to the packaging of a product".

LIST OF UPDATES FOR

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, SIXTH REVISION OCTOBER 2023

(September 2023 Updates)

6. Addition of information in 4. Examples of Types of Repacking Activity on Page 3 by –

(a) adding activity no. 19 as follows:

19.	To affix a 'QR code' label for e-labelling onto the outer carton label / immediate label	√	√	Primary/ Secondary repacker	Refer to Guideline on Electronic Labelling (E-Labelling) for Pharmaceutical Products in Malaysia

LIST OF UPDATES FOR
DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, SIXTH REVISION OCTOBER 2023
(October 2023 Updates)

There are eight (8) amendments for the October 2023 DRGD Updates as follows:

Main Body of DRGD Third Edition, Fifth Revision July 2023

Preamble

1. Addition of information, Page 1

Section B: Product Registration Process

2. Addition of information, 10. Evaluation of Application, Page 46

Section E: Post-Registration Process

3. Addition of information, 18. Maintenance of Registration, Page 55
4. Addition of information, 21.1 Pharmacovigilance, Page 66
5. Amendment of information, 21.2 Post-Market Surveillance, 21.3 Punitive Action by the Authority, 21.4 Notification of Product Quality Issue, Page 66, 67, 68

Appendix of DRGD Third Edition, Fifth Revision July 2023

Appendix 4: Guideline on Registration of Biologics

6. Deletion of information, Page 1

Appendix 20: Specific Labelling Requirements

7. Amendment of existing safety information, No. 121, Loperamide, Page 119
8. Amendment of existing safety information, No. 215, Topiramate, Page 209

LIST OF UPDATES FOR
DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, SIXTH REVISION OCTOBER 2023
(October 2023 Updates)

Amendment of Preamble

1. Amendment of information in Preamble on Page 1 by –

   (a) adding a new statement, "The National Pharmaceutical Regulatory Agency (NPRA) requirements for registration of pharmaceutical products are aligned with the guidelines and recommendations for quality, safety and efficacy of the World Health Organization (WHO) or other internationally accepted standards such as International Conference of Harmonization (ICH)."

Amendment of Section B: Product Registration Process

2. Amendment of information in 10. Evaluation of Application on Page 46 by –

   (a) adding a new statement, "NPRA applies Good Review Practices in the evaluation processes in accordance with the *World Health Organization (WHO) Technical Report Series: Good Review Practices: Guidelines for National and Regional Regulatory Authorities.*"

Amendment of Section E: Post-Registration Process

3. Amendment of information in 18. Maintenance of Registration on Page 55 by –

   (a) adding a new statement, "c) Upon DCA approval for product re-registration (renewal), the product registration is valid for five (5) years or such period as specified in the Authority database (unless the registration is suspended or cancelled by the Authority)."

4. Addition of information in 21.1 Pharmacovigilance on Page 66 by –

   (a) adding the following new paragraph,

   "**ii. Product Recall due to Serious Adverse Drug Reactions**

   In certain cases, products may need to be recalled due to reported serious adverse drug reactions. For more details regarding product recalls linked to serious adverse drug reactions, please refer to 21.2.7 ii) Product Recall."

5. Amendment of information in 21.2 Post-Market Surveillance, 21.3 Punitive Action by the Authority and 21.4 Notification of Product Quality Issue on Page 66, 67 and 68 by –

   (a) substituting 21.2 Post-Market Surveillance, 21.3 Punitive Action by the Authority and 21.4 Notification of Product Quality Issue with the following:

"21.2 Product Quality Monitoring (PQM)

Product Quality Monitoring (PQM) is conducted by NPRA to monitor the quality of registered products available in the market. The aims of PQM are to detect quality defect or non-compliant products and take necessary regulatory actions and/or measures in a timely manner to address any potential risks.

The Product Registration Holder (PRH) plays an important role to ensure that the aims of PQM are achievable. The PRH is responsible to:

i) Ensure the safety, quality and efficacy of their products in accordance with current standards and requirements determined by the Authority.
ii) Have adequate systems and appropriate procedures in place to investigate, review and report product quality-related issues to NPRA, and if necessary, to promptly recall the product from the distribution network after consultation with NPRA.
iii) Manage PQM, quality defect investigations and for deciding the measures to be taken to mitigate any potential risk(s) including recalls. Sufficient personnel and resources should be made available for the handling, reviewing, investigation of any PQM-related matters and for implementing any risk mitigation measures, as well as for the management of interactions with NPRA.

iv) Notify NPRA of any registered product quality-related issues in a timely manner. The PRH shall ensure that investigations are conducted and necessary actions and/or measures are implemented to address product quality-related issues.
v) Provide full cooperation to furnish product samples, testing materials (when requested) and relevant documents for evaluation and testing purposes, within the stipulated time as determined by NPRA.

For further information, refer to: Section C: Quality Control.

vi) Provide necessary information when requested and able to be contacted by NPRA when necessary. In situation where the PRH is uncontactable and/or failed to provide requested information, the Authority may review the registration status of the product.

Reference: *Bil. (23) dlm.BPFK/PPP/01/03 Jld 3, Pekeliling Tindakan Punitif Regulatori Ke Atas Syarikat Pemegang Pendaftaran Produk Yang Gagal Dihubungi Oleh BPFK,* (17 December 2014)

21.2.1 Product Quality Monitoring (PQM) Programme

NPRA shall monitor compliance of registered products through the Product Quality Monitoring (PQM) programme. The PQM programme for registered products consists of, among others:

i) Product sampling
ii) Product testing
iii) Monitoring of label compliance
iv) Handling of product quality reporting
v) Handling of out-of-specification (OOS) reports
vi) Monitoring of regulatory action undertaken for non-compliant products
vii) Monitoring voluntary recall
viii) Risk communication on information of product issues.

21.2.2 Product Sampling

Sampling of registered products is conducted according to the annual sampling plan (active sampling) and reactive sampling based on potential health risks to the public.

For the purpose of ensuring quality and/or label compliance, NPRA shall obtain a product sample from the PRH or the supply chain. The sample for laboratory testing must fulfil the following criteria:

i) The sample collected for a product must be from the same production batch.
ii) The sample should be presented in its originally marketed container/packaging and unopened.
iii) Unless justified, the expiry date should not be less than one (1) year from the date of sampling.
iv) Unless justified, quantity of sample should be as per requested or determined by NPRA.
v) The sample should represent product meant for local market.
vi) The integrity of each sample must be preserved during handling, storage, and transportation from the sampling sites to NPRA.

The PRH may also be requested and/or subsequently contacted to provide any further information about the product samples.

21.2.3 Product Testing

Samples are analysed at the NPRA Laboratory to verify its compliance with registered specifications and/or quality standards as stated by the pharmacopoeias.

Products are typically assessed for one or more parameters, among others: Identification, Assay, Disintegration/Dissolution, Microbiological tests, Heavy metal tests, Related substance/Impurity tests, Sterility and Screening for possible adulterants.

For further information, refer to: Section C: Quality Control.

21.2.4 Monitoring of Label Compliance

Labels and package insert of the samples will be checked to ensure compliance with the requirements determined by the Authority.

For further information, refer to*:*

Appendix 6: Guideline on Registration of Health Supplements

Appendix 7: Guideline on Registration of Natural Products

Appendix 19: General Labelling Requirements, and

Appendix 20: Specific Labelling Requirements

21.2.5 Product Quality Reporting

The PRH shall notify NPRA of any product quality-related issues of which the PRH is aware of, with complete investigation report. This includes root cause analysis and corrective action if necessary. Product quality reporting can be (non-exhaustive):

i) initiated by reports from healthcare facilities/professionals and public
ii) due to out-of-specification (OOS) during product life cycle. Once the incident is confirmed, it is recommended that reports are submitted to NPRA within 48 hours.

It is also the responsibility of the prescribers, pharmacists, as well as all other healthcare professionals to report any product quality defect or regulatory non-compliance by using the Quality Reporting of Registered Product (NPRA/435/2) form with complaint sample (if any).

All report on product quality-related issues received shall be investigated by NPRA as well as the PRH/ manufacturer. In the event of confirmed case of quality-related issues or regulatory non-compliance, NPRA may take necessary regulatory action on the product.

It is the responsibility of the PRH to determine the appropriate corrective and preventive action, as well as risk control measures such as (if appropriate/when necessary):

i) Issuance of “Dear Healthcare Professional Communication (DHPC)”
ii) A product recall
iii) Issuance of a press release
iv) Withdrawal of the product registration.

NPRA will review the information provided in the report submitted by the PRH and may request for further information required for assessment.

21.2.6 Risk Communication on Information of Product Issues

As part of regulatory network worldwide, NPRA actively participates in exchanging information on any product quality defect or regulatory non-compliance to safeguard the public health.

Aside from reports received under paragraph 21.2.5, NPRA also receives information pertaining to product quality, safety and efficacy issues from other National Regulatory Authority (NRA/NRAs). The relevant information received shall be investigated by NPRA and action will be taken accordingly.

As a risk communication measure, NPRA may disseminate information to other regulatory authority or stakeholder relating to the recall and/or other regulatory action of any product quality defect or regulatory non-compliance.

21.2.7 Regulatory Action

NPRA shall take necessary action on products that do not conform to the standards/specifications and requirements determined by the Authority. The PRH shall identify the cause of non-compliance and actions to be taken for improvement within the stipulated time.

i) Suspension and/or Cancellation of Product Registration
According to Regulation 11 of the Control of Drugs and Cosmetics Regulations 1984, the Authority may suspend or cancel the registration of any product, where deemed necessary.

The decision to suspend or cancel the registration of a product shall be made when there is actual or potential health risk to the public such as product found to contain adulterants and product with unjustified/unresolved quality issues which may affect its safety and/or efficacy.

ii) Product Recall

Product Recall means any action taken by its manufacturer, importer, and wholesaler to remove or withdraw a particular product from the market or to retrieve the product from any person to whom it has been supplied. The removal or withdrawal may be due to critical quality defects discovered which might cause health risks to users of the product.

The decision for recall of a product shall be made when there is actual or potential risk to the product users. Recalls may be done voluntarily by the PRH or as directed by the Director of Pharmaceutical Services, Ministry of Health Malaysia.

The PRH is responsible for conducting recalls of defective or unsafe products. No recall shall take place without first consulting/ informing the Authority.

The degree of recall is classified according to the severity of quality defects of the product.

	Degree I	**Degree II**	**Degree III**
Description	Products with major health risks that might cause serious injuries or death.	Products with minor health risks or are substandard.	Products with other reasons for recall that can cause health risks to users.
Notification to Authority **(for voluntary recall only)**	PRH to notify authority no later than 24 hours prior to the start of the intended voluntary recall.	PRH to notify authority no later than 48 hours prior to the start of the intended voluntary recall.	PRH to notify authority no later than 72 hours prior to the start of the intended voluntary recall.
Issuance of Communication	PRH is required to issue a	PRH is required to issue a	PRH is required to issue a

/notification to purchaser	Communication/ notification to purchaser within 24 hours of recall commencement, notifying of the recall action and providing the required instructions to purchasers, including immediate cease in sale and supply of the product.	Communication/ notification to purchaser within 48 hours of recall commencement, notifying of the recall action and providing the required instructions to purchasers, including immediate cease in sale and supply of the product.	Communication/ notification to purchaser within 72 hours of recall commencement, notifying of the recall action and providing the required instructions to purchasers, including immediate cease in sale and supply of the product.

The PRH should notify their stakeholders about the recall as soon as possible. To ensure prompt notification, the PRH may consider disseminating the recall notice to their stakeholders via telephone and/or email first and follow-up with the letter/any method of communication to confirm this notification.

The level of recall depends on the nature of problem, extent of the product's distribution and degree of hazard involved.

Level A: To all consumers (end users)

a) Usually initiated when the risk to consumers is assessed to be unacceptable, and where the product is directly supplied to consumers.

b) All wholesale and retail supply of the affected product or batch(es) should be suspended.

c) Affected product or batch(es) are to be recalled from all wholesale and retail distributors as well as consumers who had been supplied with the affected batch(es).

d) Where necessary, the recall notification to consumers may need to be done via announcement on mass media such as press announcement, newspaper notification, television and/or radio. e) The recalled product or batch(es) should be segregated in a secured area before the implementation of follow-up actions (e.g. destruction of the products).
Level B: To all points of sales a) Usually initiated when the risk to consumers is assessed to be moderate to high, but recall at consumer level is not deemed necessary. b) All wholesale and retail supply of the affected product or batch(es) should be suspended. c) Affected product or batch(es) are to be recalled from all wholesale and retail distributors including: wholesale distributors; government/private hospitals and clinics; retail pharmacies; other healthcare practitioners' establishments; nursing homes and other related institutions; and other retail outlets, e.g. health food stores, supermarkets, departmental stores.
Level C: To all distributors, wholesalers and manufacturer a) Usually initiated when the risk to consumers is assessed to be low or where other measures can be taken to mitigate the risk. b) All wholesale supply of the affected product or batch(es) should be suspended. Affected product or batch(es) are to be recalled from all affected: wholesalers; distributors; third-party logistics providers holding the product for

distribution to retailers, etc.

c) The recalled product or batch(es) should be segregated in a secured area before the implementation of follow-up actions, e.g. destruction of the products.

For further information, refer to: Chapter 7, Guidelines on Good Distribution Practice, Third Edition, 1 January 2018.

iii) Warning

The decision to issue a warning for a product shall be made when there is occurrence(s) of quality and/or regulatory non-compliance of a product, where deemed necessary.

21.2.8 Adulteration

Punitive action shall be taken against companies who are involved in adulteration. For any registered products found to have been adulterated, the following action shall be taken by the Authority:

i) The registration of the related product shall be cancelled and recall of all batches of the product shall be done immediately;
ii) The manufacturer's license of the related manufacturer shall be revoked for six (6) months for the first offence and one (1) year for the subsequent offence, from the date of the revocation letter from the Authority;
iii) All transactions (including application for product registration, application for change of PRH, application for change of manufacturing site) for the PRH involved in adulteration shall be frozen for six (6) months for the first offence and one (1) year for the subsequent offence, from the date of the cancellation letter from the Authority.

Reference: *Bil. (30) dlm.BPFK/PPP/01/03, Tindakan Punitif Ke Atas Syarikat Yang Terlibat Dengan Kes Produk Campur Palsu* (13 May 2009)"

LIST OF UPDATES FOR

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION, SIXTH REVISION OCTOBER 2023

(October 2023 Updates)

Amendment of Appendix 4: Guideline on Registration of Biologics

6. Amendment of information on Page 1 by –

(a) deleting the statement, "The National Pharmaceutical Regulatory Agency (NPRA) requirements for registration of biologics/ biopharmaceuticals products are aligned with the scientific guidelines and recommendations for quality, clinical efficacy and safety and non-clinical of the World Health Organization (WHO), European Medicines Agency (EMA) and International Conference of Harmonization (ICH)."

Amendment of Appendix 20: Specific Labelling Requirements

7. **The specific labelling requirements for existing ingredient, No. 121, Loperamide on page 119** is amended in accordance with Directive No. 10, 2023: *Direktif untuk semua produk yang mengandungi loperamide: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko pankreatitis akut (acute pancreatitis)* as decided in DCA Meeting No. 389, which takes effect on 1 November 2023 by –

(a) inserting the following statements:

"**121. LOPERAMIDE**

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing loperamide;

Package Insert

a) Adverse Effects/ Undesirable Effects:

Gastrointestinal disorders
Frequency 'not known': Acute pancreatitis

Consumer Medication Information Leaflet (RiMUP)

a) Side effects:

Upper abdominal pain, abdominal pain that radiates to back, tenderness when touching the abdomen, fever, rapid pulse, nausea, vomiting, which may be symptoms of inflammation of the pancreas.

Reference: **Directive No. 10, 2023**. *NPRA.600-1/9/13 (28) Jld.1 Direktif untuk semua produk yang mengandungi loperamide: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan risiko pankreatitis akut (acute pancreatitis)"*

8. **The specific labelling requirements for existing ingredient, No. 215, Topiramate on page 209** is amended in accordance with Directive No. 11, 2023: *Direktif untuk semua produk yang mengandungi topiramate: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan:*

i. Risiko gangguan neurodevelopmental dalam kalangan kanak-kanak yang terdedah kepada topiramate semasa kehamilan ibu
ii. Penyelarasan maklumat keselamatan berkenaan risiko kecacatan kongenital (congenital malformation)

as decided in DCA Meeting No. 389, which takes effect on 1 November 2023 by –

(a) inserting the following statements:

"**215. TOPIRAMATE**

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing topiramate;

Package Insert

a) Contraindication:

*For product indicated for migraine prophylaxis, to state:

Migraine prophylaxis: in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

b) Warnings & Precautions:

Women of childbearing potential

[Product name] may cause fetal harm when administered to a pregnant woman.

Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed and a highly effective contraceptive method used. The patient should be fully informed of the risks related to the use of topiramate during pregnancy.

[Product name] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

c) Pregnancy:

[Product name] can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems) and neurodevelopmental disorders (e.g., autism spectrum disorders and intellectual disability). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.

In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of antiepileptic drugs in combination therapy. The risk has been observed in all doses and effects were reported to be dose-dependent. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

When you must not use it

*For product indicated for migraine prophylaxis, to state:

For migraine prevention: if you are pregnant or if you are a woman of childbearing potential unless you are using effective contraception. You should talk to your doctor about the best kind of contraception to use while you are taking [Product name]. If you are not sure if the above applies to you, talk to your doctor or pharmacist before using [Product name].

*For all products containing topiramate, to state:

As with other anti-epileptic medicines, there is a risk of harm to the unborn child if [Product name] is used during pregnancy. Make sure you are very clear about the risks and the benefits of using [Product name] during pregnancy:

- If you take [Product name] during pregnancy, your baby has a higher risk for birth defects, particularly, cleft lip (split in the top lip) and cleft palate (split in the roof of the mouth). Newborn boys may also have a malformation of the penis (hypospadias). These defects can develop early in pregnancy, even before you know you are pregnant.
- Your child is also at risk for developing autism and other intellectual disabilities.
- There may be other medicines to treat your condition that have a lower risk of birth defects.
- Tell your doctor straight away if you become pregnant or planning to get pregnant while taking [Product name]. You and your doctor should decide if you will continue to take [Product name] while you are pregnant.
- It is important that you do not stop taking your medicine without first consulting your doctor.
- You should talk to your doctor about the best kind of birth control to use while you are taking [Product name]. You should use effective contraception. Before the start of treatment with [Product name], a pregnancy test should be performed. Talk to your doctor if you wish to become pregnant.

Reference: Directive No. 11, 2023. *NPRA.600-1/9/13 (29) Jld.1 Direktif untuk semua produk yang mengandungi topiramate: Pengemaskinian sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) dengan maklumat keselamatan berkaitan:*

i. Risiko gangguan neurodevelopmental dalam kalangan kanak-kanak yang terdedah kepada topiramate semasa kehamilan ibu

ii. Penyelarasan maklumat keselamatan berkenaan risiko kecacatan kongenital (congenital malformation)"