PHARMACY DEPARTMENT
Hospital Canselor Tuanku Muhriz, PPUKM
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Impurities in Angiotensin Receptor Blockers (ARBs)

Recently, several ARB-containing products were recalled by USFDA due to the presence of impurities N-nitrosodimethylamine (**NMDA**) and N-nitrosodiethylamine (**NDEA**) in the active pharmaceutical ingredients (API) and it has been classified as a **probable carcinogen**. A list of products containing *valsartan*, *irbesartan* and l*osartan* are being recalled after investigations as they contain NMDA or NDEA above a certain limit that pose an unacceptable risk to patients. Even though there is no evidence that NMDA and NDEA has caused any harm to patients at the moment, precautionary steps has been taken to prevent any further exposure to the patients. It is believed that the presence of the impurities in the API was **related to the changes in the manufacturing process**.

USFDA has published the interim limits for both NMDA and NDEA for manufacturers to use to ensure their finished drug products are safe for the patients. It is stated that consuming up to 96ng/day NMDA and 26.5ng/day NDEA is reasonably safe for human ingestion and the recalled batches of ARBs exceeded these acceptable levels. USFDA is working with manufacturers and international regulators to ensure their products are free from the impurities, and they are currently tolerating the impurities below the level established for a short period of time to avoid possible shortage of ARBs word wide. The acceptable intake is a daily exposure that results in 1:100,000 cancer risk after 10 years exposure.

The table below shows list of manufacturers and companies that were affected by the product recall (as per updated on 18/1/2019). **Please be assured that all of the recalled products are NOT registered and NOT marketed in Malaysia**.

ARBs	Manufacturer of the API	Company Affected	Impurities detected
Valsartan	Zhejiang Huahai Pharmaceuticals Co Ltd, China	Teva Pharmaceuticals USA labelled as Major Pharmaceuticals	NMDA
		Prinston Pharmaceuticals Inc. labelled as Solco Healthcare LLC	NMDA
		Teva Pharmaceuticals labelled as Actavis LLC	NMDA
		Torrent Pharmaceuticals Limited	NMDA
	Hetero Labs Limited, India	Camber Pharmaceuticals Inc.	NMDA
	Mylan Laboratories Limited	Mylan Pharmaceuticals	NDEA
		Teva Pharmaceuticals USA Inc.	NDEA
	Aurobindo Pharma Limited, India	Aurobindo Pharma Limited, India	NDEA
Irbesartan	Aurobindo Pharma Limited, India	ScieGen Pharmaceuticals labelled as Westminster Pharmaceuticals	NDEA
		ScieGen Pharmaceuticals labelled as GSMS Incorporated	NDEA
	Zhejiang Huahai Pharmaceuticals Co Ltd, China	Prinston Pharmaceuticals Inc. labelled as Solco Healthcare LLC	NDEA
Losartan	Zhejiang Huahai Pharmaceuticals Co Ltd, China	Sandoz Inc.	NDEA
	Hetero Labs Limited, India	Torrent Pharmaceuticals Limited	NDEA

Scan the QR code below to view the full list of products being recalled in the US and UK.

Irbesartan | Valsartan | Losartan

Please be reminded that :

- **Not all ARB-containing products under the listed companies were recalled** due to the presence of impurities.
- Not all ARBs contain NMDA and **NDEA**
- To advice your patients to report any adverse reaction to their healthcare providers.

Updates on the ARBs Recall In Malaysia

Based on the USFDA product recall, further investigation was done by MOH Malaysia on the ARBs.

Valsartan

Further investigations found out that there are two registered products of *valsartan* in Malaysia made from APIs supplied by Mylan Laboratories Limited, India but **not marketed in Malaysia**.

Product Name	MAL Number	Manufacturer	Current Status
Hovid-Valsartan film-coated tablet 80mg	MAL16085027AZ	Hovid Berhad	Registered but NOT marketed in Malaysia
Hovid-Valsartan film-coated tablet 160mg	MAL16085026AZ	Hovid Berhad	Registered but NOT marketed in Malaysia

Losartan

There are three registered product of *losartan* in Malaysia made from API supplied by Zhejiang Huahai Pharmaceuticals Co. Ltd. However, only one product is being marketed Malaysia. The only product so far being affected is **LOSTAD HCT 50/12.5MG Film Coated Tablet (Losartan Potassium 50mg & Hydrochlorothiazide 12.5mg).** The company has been told to stop selling and supplying the products until the company can prove that it does not contain NDEA. No further updates being published by regulatory regarding this issue.

Product Name	MAL Number	Manufacturer	Current Status
Rasoltan 50 mg film-coated tablet	MAL09072784AZ	Actavis Sdn. Bhd.	Registered but NOT marketed in Malaysia
Lostad HCT 50/12.5mg film-	**MAL12105072AZ**	**Stadpharm Sdn. Bhd.**	**Registered and marketed in Malaysia**
Lostad HCT 100/25mg film- coated tablet	MAL12105073AZ	Stadpharm Sdn. Bhd.	Registered but NOT marketed in Malaysia

It is important to inform patients that if ARBs combination products are being recalled, it is due to the ARBs - *valsartan, losartan and irbesartan* component. Other components are not affected. For example, if *valsartan/hydrochlorothiazide/amlodipine* combination product is recalled, it is due to the *valsartan* component, not *hydrochlorothiazide* and *amlodipine* component. Most importantly, **all of the affected ARBs are NOT AVAILABLE in PPUKM.** Please advice your patients to continue taking current medication and **not to withhold** any drugs without asking advices from healthcare providers.

References:

1. Fda.gov. (2018). *FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan*. [online] Available at: https://www.fda.gov/Drugs/DrugSafety/ucm613916.htm [Accessed 27 Dec. 2018].
2. Health, D. (2018). *Kenyataan Akhbar KPK 23 November 2018 – Produk Valsartan dan Losartan Yang Ditarik Balik di Amerika Syarikat Serta Situasi di Pasaran Malaysia*. National Pharmaceutical Regulatory Agency, Ministry of Health Malaysia.

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