高血壓原料藥異常事件說明：醫療人員版

自 107 年 7 月起全世界各國陸續發生數起血管張力素受體阻斷劑類 (angiotensin receptor blockers, ARBs) 降血壓藥品因含亞硝胺類不純物 (NDMA、NDEA、NMBA) 導致回收事件，此類藥品臨床上用來治療高血壓、心衰竭及糖尿病腎病變，服用此藥除了可控制血壓之外，還可改善蛋白尿排除、減緩腎功能惡化及降低冠心病病人發生心血管事件的風險，間接降低住院率及死亡率。根據現行國內外相關學會所制訂的治療指引，建議高血壓病人或合併有心肌梗塞、狹心症、心衰竭、慢性腎臟病、糖尿病等疾病者，應服用此類藥物治療。

亞硝胺類不純物是一種環境的汙染物，微量的亞硝胺類可能存在於水、肉類、乳製品、穀物及蔬菜中。根據美國食品藥物管理局的資料，以 NDMA 為例，食用醃肉中預估攝取量約 4-230 ng/日、燻肉約 4-1020 ng /日、烤肉含 6-130 ng /日、培根則約 70-90 ng /日。目前三種亞硝胺類不純物：NDMA、NDEA、NMBA，每日可接受的攝取量上限各為 96、26.5、96 ng (每日可接受的攝取量上限是依照接觸不純物 70 年後，每十萬人有一人會發生癌症的風險訂定)。另外雖然亞硝胺類被國際癌症研究機構 (International Agency for Research on Cancer, IARC) 歸類為很可能具人類致癌性的 2A 級致癌物，但目前並未有人體相關的研究證實此不純物與癌症的相關性。

根據目前檢出結果，並不是所有的 ARBs 皆含有超出標準的亞硝胺類不純物，衛生福利部食品藥物管理署已即時發布警訊，除了將問題產品下架回收、暫停輸入異常原料藥、主動採檢，並要求所有藥證持有廠商限期提供合格證明，也會同步持續蒐集各國相關資訊，以維護國人用藥安全。

若患者與您討論是否需要換藥，您可以參考以下說明進行醫病決策共享：

一、重新審視患者現有疾病：

1. 若為單純高血壓且無合併多種機轉藥品，但在已更換為目前無檢出不純物之 ARBs 後仍有疑慮者，可以考慮使用其他機轉的藥品。
2. 若併有 heart failure、diabetic nephropathy、cardiovascular risk reduction after MI 者，欲更換成 ACEIs 者，請參考附表評估該藥品是否有相關適應症，並考量 ACEIs 可能對病人造成乾咳之副作用。

二、與患者溝通使用現有品項之臨床必要性及停藥的風險。

相關治療指引：

1. FDA updates on angiotensin II receptor blocker (ARB) recalls including valsartan, losartan and irbesartan. Retrieved from https://www.fda.gov/drugs/drugsafety/ucm613916.htm#interimlimits (March 27, 2019)
2. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults. Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8).
3. 2015 Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension.
4. The 2017 Focused Update of the Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension.
5. 2018 ESC/ESH Guidelines for the management of arterial hypertension
6. 2013 ACCF/AHA Guideline for the Management of Heart Failure.
7. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure.
8. American Diabetes Association Standards of Medical Care in Diabetes- 2019.

Table. Indication Comparison of Angiotensin Agents

Reference: Lexicomp® Online (black V: approved by FDA, blue V: approved by TFDA)

ACE Inhibitors				
Drugs	**Hypertension**	**Heart failure**	**Diabetic nephropathy**	**Other indication**
Benazepril	V			
	V			
Captopril	V	Heart failure with reduced ejection fraction (HFrEF)		LV dysfunction following MI Off-label use ● Acute hypertension (urgency/emergency) ● Raynaud phenomenon
	V			
Enalapril	V	V		Asymptomatic left ventricular dysfunction
	V	V		
Fosinopril	V	V		Off-label use HIV-associated nephropathy (HIVAN)
	V	V		
Lisinopril	V	Heart failure with reduced ejection fraction (HFrEF):		ST-elevation myocardial infarction Off-label use ● Non-ST elevation acute coronary syndrome (NSTEACS) ● Posttransplant erythrocytosis (renal transplant recipients) ● Proteinuric chronic kidney disease
	V	V		V (AMI)

ACE Inhibitors				
Drugs	**Hypertension**	**Heart failure**	**Diabetic nephropathy**	**Other indication**
Perindopril	V	Off-label use		Stable coronary artery disease
	V	V		
Quinapril	V	V		
	V	V		
Ramipril	V	Heart failure post-myocardial infarction Off-label use Heart failure with reduced ejection fraction		Reduction in risk of MI, stroke, and death from cardiovascular causes
	V	V (HF post-MI)		V

Angiotensin II Receptor Blockers				
Drugs	**Hypertension**	**Heart failure**	**Diabetic nephropathy**	**Other indication**
Azilsartan	V			
	V			
Candesartan	V	V		
	V	V		
Irbesartan	V		V	
	V		V	
Losartan	V	Off-label use	V	Hypertension with left ventricular hypertrophy
	V		V	
Olmesartan	V			
	V			
Telmisartan	V			Cardiovascular risk reduction
	V			V
Valsartan	V	V		Left ventricular dysfunction or failure after MI
	V	V		V

ACE Inhibitors /Angiotensin II Receptor Blockers				
Drugs	**Hypertension**	**Heart failure**	**Diabetic nephropathy**	**Other indication**
Sacubitril/Valsart		V		

an		V		
Renin Inhibitors				
Drugs	**Hypertension**	**Heart failure**	**Diabetic nephropathy**	**Other indication**
Aliskiren	V			
	V			