

IMPORTANT MEDICINE SAFETY INFORMATION

11 February 2021

Dear Healthcare Professional

RE: INCREASED RISK OF SUBCLINICAL ACUTE INTERSTITIAL NEPHRITIS ASSOCIATED WITH THE USE OF PROTON PUMP INHIBITORS (PPIs) LEADING TO ACUTE KIDNEY INJURY AND/OR CHRONIC RENAL FAILURE

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), the below listed companies would like to inform you of an increased risk of subclinical acute nephritis associated with the use of PPIs leading to chronic renal inflammation and reduced renal function.

The Professional Information (PI) and Patient Information Leaflet (PIL) of proton pump inhibitor (PPI) containing medicines will be amended to reflect the above safety information.

Safety concern

- Acute interstitial nephritis (AIN), also called acute tubulointerstitial nephritis has been observed in patients taking PPIs and may occur at any point during PPI therapy.
- AIN is characterised by an inflammatory reaction within the tubulointerstitial space of the kidney.
- AIN can progress to acute kidney injury (acute renal failure). A delay in diagnosis and continued use of the PPI can lead to chronic renal failure.

Background on the Safety Concern

- AIN has been observed in patients taking PPIs and may occur at any point during PPI therapy. Patients may present with non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia).
- Based on a meta-analysis of seven observational studies, the use of PPIs was significantly associated with an increased risk of Acute Kidney Injury (AKI). (Adjusted Risk Ratio =

1.61%, 95% Confidence Interval: 1.16 -2.22). Most AKI events were identified specifically in the form of AIN.^[1]

- In a reported case series, renal biopsy demonstrated a diffused interstitial cellular infiltrate of eosinophils and lymphocytes with and without tubulitis, whereas the glomeruli and vasculature were normal. This occurred in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia) ^[2]

Advice to healthcare professionals

- Healthcare professionals should frequently monitor renal function and check the urine for haematuria and/or proteinuria in patients on treatment with PPIs. Patients should be advised to report any decrease in urine volumes or suspect that there is blood in their urine.
- Treatment with PPIs should be discontinued in patients with AIN.

Healthcare professionals are urged to report any adverse drug reactions (ADRs) or product quality issues to SAHPRA via the eReporting link available on the SAHPRA website (www.sahpra.org.za). Alternatively, please complete the ADR reporting form accessible via the SAHPRA website and email it to adr@sahpra.org.za. Healthcare professionals may also use the National Department of Health Mobile Application accessible from the Essential Medicines List (EML) Clinical Guide to report ADRs or product quality issues. For more information on ADR reporting of products listed below, please contact the SAHPRA vigilance unit at pvqueries@sahpra.org.za or alternatively use the contact details indicated below:

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
Cipla Medpro (Pty) Ltd	LANSOLOC OTC	Lansoprazole 15mg	37/11.4.3/0238	Tel: 021 943 4200 Fax: 021 914 1587 Email: drugsafetysa@Cipla.com
	LANSOLOC 30	Lansoprazole 30mg	37/11.4.3/0155	
	PRAZOLOC OTC	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg	43/11.4.3/1145	
	PRAZOLOC 20	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg	43/11.4.3/1147	
	PRAZOLOC 40	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg	43/11.4.3/1148	
	PRAZOLOC 40 IV	Pantoprazole sodium equivalent to pantoprazole 40 mg/ 10 ml	44/11.4.3/0305	
	LANCAP 15 MG	Lansoprazole 15 mg	A40/11.4.3/0247	Tel: 021 707 7000
	LANCAP 30 MG	Lansoprazole 30 mg	A40/11.4.3/0248	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
Pharma Dynamics (Pty) Ltd	PEPLOC OTC	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg	A42/11.4.3/0344	Fax: 021 702 0533 Email: pharmacovigilance@pharmadynamics.co.za and p.vanvuuren@pharmadynamics.co.za
	PEPLOC 20 MG	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg	A42/11.4.3/0056	
	PEPLOC 40 MG	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg	A42/11.4.3/0057	
Adcock Ingram Limited	ROZNAL OTC	Lansoprazole 15 mg	A40/11.4.3/0154	Tel: 011 635 0134 Fax: 086 553 0128 Email: Adcock.Aereports@adcock.com
	ADCO-ROZNAL	Lansoprazole 30 mg	37/11.4.3/0558	
	RAPACID	Omeprazole 10 mg	A39/11.4.3/0466	
	RAPACID 20	Omeprazole 20 mg	37/11.4.3/0228	
	ADCO OMEPRAZOLE 40	Omeprazole 40 mg	A39/11.4.3/0467	
	BURNLOC	Lansoprazole 15 mg	A39/11.4.3/0116	
Adcock Ingram Critical Care (Pty) Ltd	ADCO PANTOPRAZOLE IV	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg	44/11.4.3/0981	
Ethicare	ALTOSEC 20	Omeprazole 20 mg	32/11.4.3/0087	Tel: 0800 118 088 Fax: 011 239 6303 Email: drugsafety@aspenpharma.com
	TRUSTAN 20 MG	Esomeprazole magnesium 20 mg/	45/11.4.3/0777	
	TRUSTAN 40 MG	Esomeprazole magnesium 40 mg	45/11.4.3/0778	
	ASPEPRAZ 40 MG INJECTION	Esomeprazole sodium equivalent to 40 mg esomeprazole per vial	46/11.4.3/0079	
	ASPEN PANTOPRAZOLE 20	Pantoprazole 20 mg	43/11.4.3/0545/	
	ASPEN PANTOPRAZOLE 40	Pantoprazole 40 mg	43/11.4.3/0546	
	ASPEN PANTOPRAZOLE IV	Pantoprazole sodium sesquihydrate contains 40 mg of pantoprazole in each 10 ml vial	42/11.4.3/0313	
Forrester Pharma (Pty) Ltd	ESOTAB 20	Esomeprazole 20 mg	A50/11.4.3/0031	Tel: 021 943 0600 Fax: 021 914 2239 Email: pv@forresterpharma.com
	ESOTAB 40	Esomeprazole 40 mg	A50/11.4.3/0032	
Ranbaxy Pharmaceuticals (Pty) Ltd.	PANTOCID 20 TABLETS	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg	41/11.4.3/0787	Tel: +27 11 495 0117 Fax: +27 11 495 0150 Email:
	PANTOCID 40 TABLETS	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg	A40/11.4.3/0482	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	PANTOCID 40mg INJECTION	Pantoprazole sodium equivalent to pantoprazole 40 mg	A40/11.4.3/0072	Geeta.ghela@sunpharma.com Barryjames.lewis@sunpharma.com
	NEXIPRAZ 20	Esomeprazole magnesium equivalent to esomeprazole 20mg	43/11.4.3/0125	
	NEXIPRAZ 40	Esomeprazole magnesium equivalent to esomeprazole 40mg	43/11.4.3/0126	
	NESOPRAM 20	Esomeprazole magnesium equivalent to esomeprazole 20mg	43/11.4.3/0123	
	NESOPRAM 40	Esomeprazole magnesium equivalent to esomeprazole 40mg	43/11.4.3/0124	
	RAN-LANSOPRAZOLE 15	Lansoprazole 15mg	A39/11.4.3/0251	
	RAN-LANSOPRAZOLE 30	Lansoprazole 30mg	A39/11.4.3/0252	
SUN Pharmaceuticals S.A (Pty) Ltd.	NEXIPRAZ IV	Esomeprazole 40mg IV	46/11.4.3/0606	Tel: +27 643 2083 Fax: +27 643 2001/3 Email: Reshma.joshi@sunpharma.com Barryjames.lewis@sunpharma.com
Dr Reddy's Laboratories (Pty) Ltd	OMEZ 10	Omeprazole 10 mg	34/11.4.3/0299	Tel: 011 324 2100 Email: AdverseEvents.SA@drrreddys.com
	OMEZ 20	Omeprazole 20 mg	34/11.4.3/0300	
	OMEZ 40	Omeprazole 40 mg	34/11.4.3/0301	
	PENTOZ 20	Pantoprazole sodium sesquihydrate equivalent to Pantoprazole 20 mg.	41/11.4.3/0641	
	PENTOZ 40	Pantoprazole sodium sesquihydrate equivalent to Pantoprazole 40 mg	41/11.4.3/0642	
	PENTOZ OTC	Pantoprazole sodium sesquihydrate equivalent to Pantoprazole 20 mg.	45/11.4.3/0592	
Xixia Pharmaceuticals (Pty) Ltd	MYLAN PANTOPRAZOLE 20 MG	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 20 mg	43/11.4.3/0843	Tel: 071 281 2503 Email: medinfos@mylan.com
	MYLAN PANTOPRAZOLE 40 MG	Pantoprazole sodium sesquihydrate equivalent to pantoprazole 40 mg	43/11.4.3/0844	

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
[Marketed by Mylan (Pty) Ltd]				
Teva Pharmaceuticals (Pty) Ltd	LOKIT	Omeprazole 20 mg	36/11.4.3/0446	Tel: 011 055 0200 Fax: 011 388 2688 Email: Safety.South-Africa@teva.co.il
Dezzo Trading 392 (Pty) Ltd	NOZER (Capsules)	Omeprazole 20 mg	36/11.4.2/0420	Tel: 011 075 8909 082 421 5817 Fax: 086 664 6223 Email: dawn.keswa@ascendishhealth.com
Unicorn Pharmaceuticals (Pty) Ltd	LANSOPRAZOLE UNICORN 15	Lansoprazole 15 mg	A40/11.4.3/0249	Tel: 021 460 6572 Fax: 021 467 3952 Email: enquiries@unicornpharma.co.za
	LANSOPRAZOLE UNICORN 30	Lansoprazole 30 mg	A40/11.4.3/0250	
Sandoz SA (Pty) Ltd	NEXMEZOL 20	Esomeprazole magnesium dihydrate	44/11.4.3/0335	Tel: +27 11 347 6600 Email: patientsafety.sacg@novartis.com Web: https://www.report.novartis.com/
	NEXMEZOL 40	Esomeprazole magnesium dihydrate	44/11.4.3/0336	
	NEXOMEPE 20	Esomeprazole magnesium dihydrate	44/11.4.3/0337	
	NEXOMEPE 40	Esomeprazole magnesium dihydrate	44/11.4.3/0338	
	SANDOZ OMEPRAZOLE 20	Omeprazole	36/11.4.3/0430	
	OMIFLUX 20	Omeprazole	43/11.4.3/0457	
	PROBITOR 20	Omeprazole	43/11.4.3/0458	
	TOPRAFLUX IV	Pantoprazole sodium sesquihydrate	41/11.4.3/0345	
	PANTOPRAZOLE UNICORN 20	Pantoprazole sodium sesquihydrate	43/11.4.3/0485	
	PANTOPRAZOLE UNICORN 40	Pantoprazole sodium sesquihydrate	43/11.4.3/0486	
	TOPRAFLUX 20	Pantoprazole sodium sesquihydrate	43/11.4.3/0483	
	TOPRAFLUX 40	Pantoprazole sodium sesquihydrate	43/11.4.3/0484	
	RABEMED 10	Rabeprazole sodium	44/11.4.3/0597	
RABEMED 20	Rabeprazole sodium	44/11.4.3/0598		

Yours faithfully

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References:

1. Yang Y et al. 2017. Proton-pump inhibitors use, and risk of acute kidney injury: a meta-analysis of observational studies. *Drug Design, Development & Therapy*. Vol 11, pg. 1291-1299

2. Brewster UC. Perazella MA. 2007. Proton Pump Inhibitors and the kidney: critical review. *Clinical Nephrology*. Vol 68 (2), pg. 65-72