



IMPORTANT MEDICINE SAFETY INFORMATION GABAPENTINOIDS – RISK OF SERIOUS BREATHING DIFFICULTY

03 April 2023

Dear Healthcare Professional

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), the below listed companies (logo's above), would like to inform you about the risk of serious breathing difficulty associated with the use of gabapentinoids (gabapentin and pregabalin).

The Professional Information (PI) and Patient Information Leaflet (PIL) of gabapentin and pregabalin containing medicines will be updated to appropriately reflect the above safety information.

Summary

- There are cases of respiratory depression and dyspnoea associated with the use of gabapentinoids reported globally.
- Importantly, data reveals that when gabapentinoids were given concomitantly with opioids, they potentiate the respiratory depressant effect of opioids especially in patients with risk factors such as, advanced age, renal dysfunction, respiratory conditions as well as co-administration with other central nervous system (CNS) depressants. Dose adjustments of the opioids should be considered in these patients.

Background on the safety concern

Gabapentin and pregabalin, jointly referred to as gabapentinoids, are commonly used nonopioid analgesics. They are indicated for partial seizures with and without secondary generalisation.

Gabapentinoids are commonly co-administered with opioids for prescribed medical uses and abused in combination with opioids. Due to their mechanism of action in the CNS, they are prone to misuse, abuse, and dependence. Respiratory depression, due to gabapentin and pregabalin has been emerging for the past few years even in patients who were not concurrently on opioids. Post-

marketing studies showed similar effects among patients taking these medications simultaneously with other respiratory suppressants.

U.S. Food Drug and Administration (FDA) issued a Drug Safety Communication (published on the 19th of December 2019) regarding serious breathing difficulties which may occur in patients using gabapentin or pregabalin who have respiratory risk factors (including the use of opioid pain medicines and other drugs that depress the CNS, and conditions that reduce lung function such as chronic obstructive pulmonary disease (COPD)).

Several sources of data, including case reports submitted to FDA Adverse Event Reporting System (FAERS) database emphasize the risk. Forty-nine (49) respiratory depression case reports were found on FAERS database, these cases were reviewed over the 5-year period from 2012 to 2017. Of these 49 reports, 12 (24%) led to death. Other small-randomized trials also provided evidence that gabapentinoids alone and in combination with opioids resulted in depression of respiratory function.

Advice to healthcare professionals

- Healthcare professionals are advised to start gabapentinoids at the lowest dose and monitor patients for symptoms of respiratory depression and sedation when co-prescribing gabapentinoids with an opioid or other CNS depressant such as a benzodiazepine.
- Patients with underlying respiratory disease, renal dysfunction and elderly patients are at increased risk and should be managed similarly.
- The management of respiratory depression should include close observation, supportive measures, and reduction or withdrawal of CNS depressants, including the gabapentinoids used for analgesia or seizure control. Gabapentinoids should be tapered prior to discontinuation.
- Patients and care givers should be advised to look out for symptoms of respiratory depression that may arise. These symptoms may include but are not limited to the following: confusion (disorientation), dizziness, shallow or difficult breathing, unresponsiveness (sleepiness or lethargy) and bluish coloured skin.
- Patients should be encouraged to consult their healthcare professional immediately when planning to stop the use of gabapentin or pregabalin containing medicines.
- Healthcare professionals are urged to report any adverse drug reactions (ADRs), or product quality issues (including batch details) associated with the use of the listed products to the companies below, or to SAHPRA via the eReporting link available on the SAHPRA website (www.sahpra.org.za).
- Alternatively, healthcare professionals may complete the ADR reporting form accessible via the SAHPRA website and email it to adr@sahpra.org.za . Additionally, reporting can be done via Med Safety App. The App can be downloaded into a smart mobile phone through Google Play or App Store. For more information on Med Safety App, please visit SAHPRA website.
- For more information on ADR reporting of products listed below, please contact SAHPRA Vigilance unit at pvqueries@sahpra.org.za or alternatively use the contact details indicated in below:








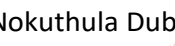
Details for the respective companies are indicated in the table below:

Company	Product	Active ingredient	Registration Number	Contact details
Ranbaxy Pharmaceuticals (Pty) Ltd	Lybet 25	Pregabalin	47/2.5/1235	Responsible Pharmacist: Geeta Ghela Email: Geeta.Ghela@sunpharma.com 011 495 0181
	Lybet 75	Pregabalin	47/2.5/1236	
	Lybet 150	Pregabalin	47/2.5/1237	
	Pregabalin 25 Sun Pharma	Pregabalin	48/2.5/0333	
	Pregabalin 75 Sun Pharma	Pregabalin	48/2.5/0334	
	Pregabalin 150 Sun Pharma	Pregabalin	48/2.5/0335	
Ranbaxy Pharmaceuticals (Pty) Ltd	Epleptin 100 mg	Gabapentin	A40/2.5/0158	Responsible Pharmacist: Geeta Ghela Email: Geeta.Ghela@sunpharma.com 011 495 0181
	Epleptin 300 mg	Gabapentin	A40/2.5/0159	
	Epleptin 400 mg	Gabapentin	A40/2.5/0160	
Teva Pharmaceuticals (PTY) Ltd	Nurika 25 mg	Pregabalin	46/2.5/0772.764	Email: Safety.South-Africa@teva.co.il Tel: 011 055 0200 Fax: 011 388 2688
	Nurika 50 mg	Pregabalin	46/2.5/0773.765	
	Nurika 75 mg	Pregabalin	46/2.5/0774.766	
	Nurika 150 mg	Pregabalin	46/2.5/0775.767	
	Pregabalin Ivax 25 mg	Pregabalin	46/2.5/0764	
	Pregabalin Ivax 50 mg	Pregabalin	46/2.5/0765	
	Pregabalin Ivax 75 mg	Pregabalin	46/2.5/0766	
	Pregabalin Ivax 150 mg	Pregabalin	46/2.5/0767	
Pharma Dynamics (Pty) Ltd	Myalica 25 mg	Pregabalin	49/2.5/0180	Email: pharmacovigilance@pharmadynamics.co.za Tel: 021 707 7000 Fax: 021 702 0533
	Myalica 75 mg	Pregabalin	49/2.5/0182	
	Myalica 150 mg	Pregabalin	49/2.5/0184	
Aurogen South Africa (Pty) Ltd	Nergil 25 mg	Pregabalin	48/2.5/1073	Responsible Pharmacist: Samantha Pillay Chengiah samantha.chengiah@aurogensa.co.za
	Nergil 75 mg	Pregabalin	48/2.5/1074	
	Nergil 150 mg	Pregabalin	48/2.5/1075	

Company	Product	Active ingredient	Registration Number	Contact details
Biotech Laboratories (Pty) Ltd	Pregabalin 25 Biotech	Pregabalin	50/2.5/0371	Responsible Pharmacist: Motshabi Kgantsi motshabi@biotechlabs.co.za 011 848 3050
	Pregabalin 75 Biotech	Pregabalin	50/2.5/0372	
	Pregabalin 150 Biotech	Pregabalin	50/2.5/0373	
Biotech Laboratories (Pty) Ltd	Biotech Gabapentin 100	Gabapentin	43/2.5/0332	Responsible Pharmacist: Motshabi Kgantsi motshabi@biotechlabs.co.za 011 848 3050
	Biotech Gabapentin 300	Gabapentin	43/2.5/0329	
	Biotech Gabapentin 400	Gabapentin	43/2.5/0333	
Cipla Medpro (Pty) Ltd	Pregabalin 25 Cipla	Pregabalin	50/2.5/0601	Responsible Pharmacist: Praba Thandrind Praba.Thandrind@Cipla.com & drugsafetysa@cipla.com Tel: 021 943 4200
	Pregabalin 75 Cipla	Pregabalin	50/2.5/0602	
	Pregabalin 150 Cipla	Pregabalin	50/2.5/0603	
Oethmaan Biosims (Pty) Ltd	Gabapentin 100 Oethmaan	Gabapentin	A39/2.5/0432	Deputy Responsible Pharmacist: Shahaboodeen Charfaray regulatory@oethmaan.co.za 011 433 0602
	Gabapentin 300 Oethmaan	Gabapentin	A39/2.5/0433	
	Gabapentin 400 Oethmaan	Gabapentin	A39/2.5/0434	
Hetero Drugs SA (Pty) Ltd.	Anzabal 25	Pregabalin	51/2.5/0203	Responsible Pharmacist / RA/QA Head Nokuthula Dube Nokuthula.n@hetero.com +27 12 644 1220
	Anzabal 50	Pregabalin	51/2.5/0204	
	Anzabal 75	Pregabalin	51/2.5/0205	
	Anzabal 100	Pregabalin	51/2.5/0206	
	Anzabal 150	Pregabalin	51/2.5/0207	
	Neubabur 25	Pregabalin	51/2.5/0211	
	Neubabur 50	Pregabalin	51/2.5/0212	
	Neubabur 75	Pregabalin	51/2.5/0213	
	Neubabur 100	Pregabalin	51/2.5/0214	
	Neubabur 150	Pregabalin	51/2.5/0215	
Neviprasy 25	Pregabalin	51/2.5/0219		

Company	Product	Active ingredient	Registration Number	Contact details
	Neviprasy 50	Pregabalin	51/2.5/0220	
	Neviprasy 75	Pregabalin	51/2.5/0221	
	Neviprasy 100	Pregabalin	51/2.5/0222	
	Neviprasy 150	Pregabalin	51/2.5/0223	
Viatrix Healthcare (Pty) Ltd	Pregabalin Mylan 150 mg	Pregabalin	46/2.5/0221	Responsible Pharmacist: Ansie Savrda ansie.savrda@viatrix.com (+27) 11 451 1332
	Pregabalin Mylan 25 mg	Pregabalin	46/2.5/0219	
	Pregabalin Mylan 75 mg	Pregabalin	46/2.5/0220	
	Lyrica 25 mg	Pregabalin	A39/2.5/026 4	
	Lyrica 75 mg	Pregabalin	A39/2.5/026 6	
	Lyrica 150 mg	Pregabalin	A39/2.5/026 8	
	Neurontin 100	Gabapentin	27/2.5/0598	
	Neurontin 300	Gabapentin	27/2.5/0599	
	Neurontin 400	Gabapentin	27/2.5/0600	
Neurontin 600	Gabapentin	35/2.5/0099		
Forrester Pharma (Pty) Ltd	NUBACAP 25	Pregabalin 25 mg	48/2.5/1339	Responsible Pharmacist: Fatima Booysen fatima.booysen@forresterpharma.com pv@forresterpharma.com (+27) 21 943 0600
	NUBACAP 75	Pregabalin 75 mg	48/2.5/1340	
	NUBACAP 150	Pregabalin 150 mg	48/2.5/1341	
	ZANERVA 25	Pregabalin 25 mg	48/2.5/1336	
	ZANERVA 75	Pregabalin 75 mg	48/2.5/1337	
	ZANERVA 150	Pregabalin 150 mg	48/2.5/1338	

Yours sincerely,

<p>Geeta Ghela Responsible Pharmacist/QA Head Ranbaxy Pharmaceuticals (Pty) Ltd.</p> <p>Signature:  Digitally signed by Geeta Ghela DN: cn=Geeta Ghela, o=Responsible Pharmacist, ou=Ranbaxy Pharmaceuticals(pty)ltd, email=Geeta.Ghela@sunpharma.com, c=ZA Date: 2023.04.05 13:09:04 +02'00'</p>	<p>Petra van Vuuren Deputy Responsible Pharmacist Pharmadynamics (Pty) Ltd</p> <p>Signature:  Digitally signed by Petra Van Vuuren Location: Divisional Manager: Pharma Dynamics (Pty) Ltd Compliance & Pharmacovigilance, Date: 2023.04.06 10:29:58 +02'00'</p>	<p>Samantha Pillay Chengiah Responsible Pharmacist Aurogen South Africa (Pty) Ltd.</p> <p>Signature:  Digitally signed by samantha.chengiah@aurogen.com DN: cn=Samantha Chengiah, o=Aurogen South Africa (Pty) Ltd, ou=Pharmacist, c=ZA Date: 2023.04.06 10:29:58 +02'00'</p>
<p>Motshabi Kgantsi Responsible Pharmacist Biotech Laboratories (Pty) Ltd</p> <p>Signature:  Digitally signed by Motshabi Kgantsi Date: 2023.04.06 13:52:01 +02'00'</p>	<p>Salomie Keyser Responsible Pharmacist Teva Pharmaceuticals (Pty) Ltd.</p> <p>Signature:  Digitally signed by Salomie Keyser Date: 2023.04.12 14:41:21 +02'00'</p>	<p>Praba Thandrind Responsible Pharmacist: Cipla Medpro (Pty) Ltd</p> <p>Signature:  Digitally signed by Praba Thandrind Date: 2023.04.12 14:25:50 +02'00'</p>
<p>Shahaboodeen Charfaray Deputy Responsible Pharmacist Oethmaan Biosims (Pty) Ltd.</p> <p>Signature:  Digitally signed by Shahaboodeen Charfaray DN: cn=Shahaboodeen Charfaray, o=Oethmaan Biosims (Pty) Ltd, ou=SA Manager, email=regulatory@oethmaan.co.za, c=ZA Date: 2023.04.13 06:47:19 +02'00'</p>	<p>Nokuthula Dube Responsible Pharmacist / RA/QA Head Hetero Drugs SA (Pty) Ltd.</p> <p>Signature:  Digitally signed by Nokuthula Dube Date: 2023.04.13 14:12:53 +02'00'</p>	<p>Pranesh Ramadene Deputy Responsible Pharmacist Viatrix Healthcare (Pty) Ltd</p> <p>Signature:</p>
<p>Fatima Booyen Responsible Pharmacist Forrester Pharma (Pty) Ltd.</p> <p>Signature:</p>		

References

1. PRAC recommendations on signals Adopted at the 6-9 June 2017 PRAC meeting; Gabapentin – Respiratory depression without concomitant opioid use.
2. FDA Drug safety communication 2019 Sep 12; FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) When used with CNS depressants or in patients with lung problems.
3. Shrestha S, Palaian S. Respiratory concerns of gabapentin and pregabalin: What does it mean to the pharmacovigilance systems in developing countries? *F1000Res.* 2021 Feb 25;9:32. doi: 10.12688/f1000research.21962.2. PMID: PMC7919607.
4. Savelloni J, Gunter H, Lee KC, Hsu C, Yi C, Edmonds KP, Furnish T, Atayee RS. Risk of respiratory depression with opioids and concomitant gabapentinoids. *J Pain Res.* 2017;10:2635-2641 <https://doi.org/10.2147/JPR.S144963>.
5. Hahn Jongsung, Jo Youngkwon, Yoo So Hee, Shin Jaekyu, Yu Yun Mi, Ah Young-Mi; Risk of major adverse events associated with gabapentinoid and opioid combination therapy: A systematic review and meta-analysis; *Front. Pharmacol.*, 2022; <https://www.frontiersin.org/articles/10.3389/fphar.2022.1009950>.