



IMPORTANT MEDICINE SAFETY INFORMATION

09 October 2020

Dear Healthcare Professional

Re: RISK OF DOPAMINE DYSREGULATION SYNDROME ASSOCIATED WITH THE USE OF DOPAMINERGIC MEDICINES USED FOR THE TREATMENT OF PARKINSON'S DISEASE

The pharmaceutical companies mentioned below, in collaboration with South African Health Products Regulatory Authority (SAHPRA), wish to inform you of the risk of dopamine dysregulation syndrome (DDS) associated with the chronic use of dopaminergic medicines used for the treatment of Parkinson's disease. The Professional Information (PI) and Patient Information Leaflet (PIL) of these products will be amended to reflect this safety issue.

SUMMARY

Dopamine dysregulation syndrome (DDS) is an addictive disorder that may occur with chronic use of all dopaminergic medicines. Dopamine replacement therapy (DRT), with the dopamine precursor levodopa or synthetic dopamine agonists, is considered the mainstem of the pharmacological approach for the symptoms of Parkinson's disease. Patients on dopamine replacement may experience side effects such as DDS. The most common symptom of DDS is compulsive craving of Parkinson's medication, even if no symptoms of parkinsonism are present. People suffering from DDS, without the medication, may feel depressed or fatigued but become euphoric or grandiose when on the medication.

BACKGROUND TO SAFETY CONCERN

The safety concern emanated from the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) recommendation of 2017 on the risk of DDS associated with the use of carbidopa/levodopa. Following PRAC's recommendations, a review on all the dopaminergic medicines was conducted and documented evidence that DDS may occur with chronic use of all dopaminergic medicines was found.

Medicines affected by this safety concern in South Africa include bromocriptine, ropinirole, cabergoline, apomorphine, rotigoline, levodopa / carbidopa , levodopa /benserazide and pramipexole.

ADVICE TO HEALTHCARE PROFESSIONALS

- DDS is an addictive disorder and described as a compulsive pattern of dopaminergic medication misuse above doses adequate to control motor symptoms.
- The risk of DDS may occur in patients on chronic treatment with dopaminergic medicines used for Parkinson's disease.
- DDS consists of a series of complications such as compulsive use of dopaminergic medications, aggressive or hypomanic behaviours during excessive use, and withdrawal states characterised by dysphoria and anxiety, caused by long-term dopaminergic treatment in patients with Parkinson's disease.
- Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

Healthcare professionals are urged to report any adverse drug reactions (ADRs) or product quality issues associated with the use of all dopaminergic medicines to the applicable companies below or to SAHPRA Pharmacovigilance unit 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 at <https://www.sahpra.org.za/documents/12e54dcaADRForms.pdf> and email it to adr@sahpra.org.za or fax to (021) 448 6181. For more information on ADR reporting, of below listed dopaminergic medicines used for the treatment of Parkinson's disease, please call the National Adverse Events Monitoring Centre (NADEMC) on (021) 447 1618.

For further information, kindly use the contact details indicated in the table below:

Table 1: Products and contact details of companies of dopaminergic medicines

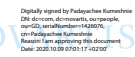
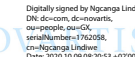
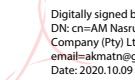
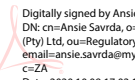
COMPANY	PRODUCT	ACTIVE INGREDIENT	REGISTRATION NUMBER	CONTACT DETAILS
Novartis South Africa (Pty) Ltd	STALEVO 50/12,5 STALEVO 100/25 STALEVO 150/37,5	Carbidopa/ levodopa/ entacapone	38/5.4.1/0067 38/5.4.1/0138 38/5.4.1/0137	Tel: +2711 347 6600 Fax: +27 11 929 2262 E-mail: patientsafety.sacg@novartis.com Web: https://www.report.novartis.com/
Sandoz South Africa (Pty) Ltd.	Pramiola 0,25	Pramipexole dihydrochloride monohydrate 0,25 mg	43/5.4.1/0855	Tel: +27 11 347 6600 Fax: +27 11 929 2262

	Pramiola 0,125	Pramipexole dihydrochloride monohydrate 0,125 mg	43/5.4.1/0856	E-mail: Patientsafety.sacg@novartis.com
Gulf Drug Company (Pty) Ltd	Oxpola 0,125 mg	Pramipexole dihydrochloride monohydrate 0,125 mg	43/5.4.1/0134	Tel: +27 31 538 8700 Fax: + 27 31 502 2379 Email: info@gulfdrug.co.za
	Oxpola 0,25 mg	Pramipexole dihydrochloride monohydrate 0,25 mg	43/5.4.1/0133	
	Oxpola 1,0 mg	Pramipexole dihydrochloride monohydrate 1,0 mg	43/5.4.1/0135	
Mylan (Pty) Ltd	Mylan Pramipexole 0,125 mg	Pramipexole dihydrochloride monohydrate 0,125 mg	45/5.4.1/0254	Tel: +27 71 281 2503 Fax: +27 11 451 1400 Email: medinfosa@mylan.com
	Mylan Pramipexole 0,25 mg	Pramipexole dihydrochloride monohydrate 0,25 mg	45/5.4.1/0255	
	Mylan Pramipexole 1,0 mg	Pramipexole dihydrochloride monohydrate 1,0 mg	45/5.4.1/0256	
Zydus Healthcare SA (Pty) Ltd	Zymipex 0.25	Pramipexole dihydrochloride monohydrate 0,25 mg	45/5.4.1/0233	Tel: +27 12 748 6400 Fax: + 27 12 748 6444 Email: medicinesafety@zydus.co.za
	Zymipex 1	Pramipexole dihydrochloride monohydrate 1,0 mg	45/5.4.1/0234	

Reference

1. Kummer A et al, Arq. Neuro-Psiquiatr. vol.64 no.4 Dec. 2006:1019-1022. Dopamine Dysregulation Syndrome in Parkinson's disease.
https://www.scielo.br/scielo.php?pid=S0004282X2006000600026&script=sci_arttext (Accessed 19 June 2020).
2. Pressman P et al., Very Well Health. Dopamine Dysregulation Syndrome. A Rare Complication of Parkinson's disease Medications <https://www.verywellhealth.com/dopamine-dysregulationsyndrome-2488783> (Updated on 15 January 2020, Accessed on 19 June 2020).
3. Warren et al., 2017 J Neurol Neurosurg Psychiatry; 88(12): 1060-1064
<https://pubmed.ncbi.nlm.nih.gov/29018160/> (Accessed 04 August 2020).

Yours sincerely,

<p><u>Kumeshnie Padayachee</u> Responsible Pharmacist Novartis South Africa (Pty) Ltd</p>	<p>Signature</p> <p>Padayachee Kumeshnie</p>  <p><small>Digitally signed by Padayachee Kumeshnie DN: cn=Kumeshnie Padayachee, o=Novartis, ou=Regulatory, email=Kumeshnie.Padayachee@novartis.com, c=ZA, serialNumber=1426076, Reason: I am approving this document Date: 2020.10.09 09:51:17 +0200'</small></p>
<p><u>Lindiwe Ngcanga</u> Responsible Pharmacist Sandoz SA (Pty) Ltd</p>	<p>Signature</p> <p>Ngcanga Lindiwe</p>  <p><small>Digitally signed by Ngcanga Lindiwe DN: cn=Lindiwe Ngcanga, o=Sandoz, ou=Regulatory, email=Lindiwe.Ngcanga@sandoz.co.za, c=ZA, serialNumber=1762058, Reason: I am approving this document Date: 2020.10.09 08:20:53 +0200'</small></p>
<p><u>Akmat M. Nasrullah</u> Responsible Pharmacist Gulf Drug Company (Pty) Ltd</p>	<p>Signature:</p> <p>AM Nasrullah</p>  <p><small>Digitally signed by AM Nasrullah DN: cn=AM Nasrullah, o=Gulf Drug Company (Pty) Ltd, ou=Regulatory, email=akmatn@gulfdrug.co.za, c=ZA, Reason: I am approving this document Date: 2020.10.09 08:44:37 +0200'</small></p>
<p><u>Ansie Savrda</u> Responsible Pharmacist Mylan (Pty) Ltd</p>	<p>Signature:</p> <p>Ansie Savrda</p>  <p><small>Digitally signed by Ansie Savrda DN: cn=Ansie Savrda, o=Mylan (Pty) Ltd, ou=Regulatory Affairs, email=ansie.savrda@mylan.com, c=ZA, Reason: I am approving this document Date: 2020.10.09 17:02:12 +0200'</small></p>
<p><u>Madhu B Swarna</u> Responsible Pharmacist Zydus Healthcare SA (Pty) Ltd</p>	<p>Signature:</p> 