IMPORTANT MEDICINE SAFETY INFORMATION

29 June 2020

Dear Healthcare Professional

Re: WARNING ABOUT CEREBRO-VASCULAR EVENTS, CEREBRO-VASCULAR ACCIDENT, CEREBRAL INFARCTION, ISCHAEMIC STROKE AND TRANSCIENT ISCHAEMIC ATTACK ASSOCIATED WITH THE USE OF TYROSINE KINASE INHIBITOR CONTAINING MEDICINES.

The pharmaceutical companies mentioned below, in collaboration with South African Health Products Regulatory Authority (SAHPRA), wish to inform you of the class related cerebrovascular adverse events reported with the use of tyrosine kinase inhibitor (TKI) containing medicines. The Professional Information (PI) and Patient Information Leaflet (PIL) of these products will be amended to reflect this safety issue.

SUMMARY

Cerebrovascular adverse events identified as class related adverse events have occurred in patients treated with TKI containing medicines. These class related cerebrovascular adverse events, shared to a variable degree by all TKIs, are cerebrovascular accident (CA), transient ischaemic attack (TIA), ischaemic stroke (IS), and cerebral infarction (CI. These cerebrovascular events may occur in patients on treatment with TKIs with or without risk factors for these events and may occur at any time during treatment with TKIs.

BACKGROUND TO SAFETY CONCERN

TKI containing medicines may have different kinase inhibition profiles and/or off target binding profiles, with some TKIs approved for very similar indications and others approved for different indications. Although many adverse events/side effects/toxicities could not be explained by a class related adverse event or a related off-target kinase inhibition effect, there is some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events.

SAHPRA conducted a qualitative search overview on VigiLyze® using the single drug name (proprietary name) and the reaction, * ischaemic central nervous system. SAHPRA noted that trends seen in the data analysis (see table 1 below) indicates that the ischaemic central nervous system reactions occur across tyrosine kinase inhibitors.

Table 1: Ischaemic Central Nervous System Vascular Condition Associated with Tyrosine Kinase Inhibitors

Drug	Period	Cases	Cerebro-vascular Accident	Transient Ischaemic Attack	Cerebral Infarction	Ischaemic Stroke
Ibrutinib	2014 till 6/3/2020	545	323	132	16	29
Dasatanib	2008 till 6/3/2020	130	70	10	16	11
Sunitinib	2008 till 6/3/2020	416	216	80	42	32
Erlotinib	2003 till 6/3/2020	385	224	40	56	20
Pazopanib	2008 till 6/3/2020	243	139	50	24	17
Imatinib	2002 till 6/3/2020	464	277	44	71	18
Nilotinib	2006 till 6/3/2020	734	341	90	146	47

References: A qualitative search overview was conducted from VigiLyze® (VigiBase database) using the single drug name (propriety name) and MedDRA (version 22.0) SMQ* Ischaemic central nervous system vascular conditions (narrow) with results shown in table 1.

ADVICE TO HEALTHCARE PROFESSIONALS

- The above mentioned cerebrovascular adverse events may occur in patients on treatment with TKI containing medicines with or without risk factors for these events and may occur at any time during treatment with TKIs.
- Patients on treatment with TKI containing medicine should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.
- Treatment with TKI containing medicines should be discontinued, and alternative treatment options be considered in patients who develop these class related cerebrovascular adverse events.

Healthcare professionals are urged to report all suspected adverse events associated with all TKI containing medicines to the applicable companies below or 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 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, please call the SAHPRA vigilance unit on (012) 842 7609/10 or National Adverse Events Monitoring Centre (NADEMC) on (021) 447 1618.

Table 2: Products and contact details of Tyrosine kinase inhibitors (TKIs) Companies

COMPANY	PRODUCT	ACTIVE INGREDIENT	REGISTRATION NUMBER	CONTACT DETAILS
Janssen Pharmaceutica (Pty) Ltd	IMBRUVICA 140 mg capsules	Ibrutinib	50/26/0939	**Tel:** +2711 518 7000 **Fax:** 011 5187104 **E-mail:** RA-JACZA-MedInfo@its.jnj.com **Web:** www.janssen.com
Ranbaxy Pharmaceuticals (Pty) Ltd a SUN PHARMA company	SUNMATIN 100 SUNMATIN 400 film coated tablets	Imatinib	44/26/0886 44/26/0887	**Tel: +27 11 495 0117** **Fax: +27 11 495 0150** **Email:** Geeta.ghela@sunpharma.com Barryjames.lewis@sunpharma.com pharmacovigilance@africasme@sunpharma.com **Web:** www.sunpharma.com
Accord Healthcare (Pty) Ltd	IMATINIB ACCORD 100 & 400 mg film coated tablets MIVESTA 100 mg MIVESTA 400 mg film coated tablets	Imatinib Imatinib	49/26/0740; 49/26/0741; 49/26/0742; 49/26/0743	Tel: +2711 234 5950 Email: medinfo@accordhealth.co.za
Pfizer Laboratories (PTY) Ltd	SUTENT 12,5 mg SUTENT 25 mg SUTENT 50 mg capsules	Sunitinib	41/26/0197 41/26/0195 41/26/0196	Tel: 0860 PFIZER (0860 734937) e-mail: ZAF.AEReporting@pfizer.com
Roche Products (Pty) Ltd	TARCEVA® 25 mg TARCEVA® 100 mg TARCEVA® 150 mg tablets	Erlotinib	A40/26/0359 A40/26/0360 A40/26/0361	**Tel:** +2711 502 5000/5183 **Fax:** +27 11 268 5748 **E-mail:** south_africa.drugsafety@roche.com illovo.regulatory_affairs@roche.com
Cipla Medpro (Pty) Ltd	IMAVEC 100 IMAVEC 400	Imatinib mesylate	42/34/0496 50/34/0118	**Tel:** 021 943 4200 / 080 222 6662 **Email:** drugsafetysa@cipla.com
Novartis South Africa (Pty) Ltd	GLEEVEC 50 mg, hard capsules GLEEVEC 100 mg GLEEVEC 400 mg Film-coated tablet	Imatinib Imatinib	36/34/0138 38/34/0143 38/34/0144	**Tel:** +2711 347 6600 **Fax:** +27 11 929 2262 **E-mail:** patientsafety.sacg@novartis.com **Web:** https://www.report.novartis.com/
Novartis South Africa (Pty) Ltd	VATIVIO 100 mg, hard capsules VATIVIO 100 mg VATIVIO 400 mg Film-coated tablet	Imatinib Imatinib	36/34/0139 46/26/0367 46/26/0368	**Tel:** +2711 347 6600 **Fax**: +27 11 929 2262 **E-mail**: patientsafety.sacg@novartis.com **Web:** https://www.report.novartis.com/
Novartis South Africa (Pty) Ltd	TASIGNA 150 mg, TASIGNA 200 mg, capsules Nilotinib 150 mg Novartis, capsules Nilotinib 200 mg Novartis, capsules	Nilotinib Nilotinib Nilotinib	45/26/0410 41/26/0973 50/26/0452 50/26/0453	**Tel:** +2711 347 6600 **Fax:** +27 11 929 2262 **E-mail:** patientsafety.sacg@novartis.com **Web:** https://www.report.novartis.com/

Novartis South Africa (Pty) Ltd	VOTRIENT 200 mg Film-coated tablet	Pazopanib	44/26/0348	**Tel:** +2711 347 6600 **Fax:** +27 11 929 2262 **E-mail:** patientsafety.sacg@novartis.com **Web:** https://www.report.novartis.com/
	VOTRIENT 400 mg Film-coated tablet	Pazopanib	44/26/0349	
	PATORMA 200 mg Film-coated tablet	Pazopanib	44/26/0346	
	PATORMA 400 mg Film-coated tablet	Pazopanib	44/26/0347	

Yours sincerely

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