IMPORTANT MEDICINE SAFETY INFORMATION

28 July 2020

Dear Healthcare Professional

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

In collaboration with the Namibia Medicines Regulatory Council (NMRC), Roche Products (Pty) Ltd wishes 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 Tarceva (erlotinib) 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.

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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 NMRC via the eReporting link available on the NMRC website (https://nmrc.gov.na) or at https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=NA.

Alternatively, please complete the ADR reporting form accessible via the NMRC website at https://nmrc.gov.na/downloads and Fax2Mail: 0886606781 or Email: info.TIPC@mhss.gov.na. For more information on ADR reporting, please call the TIPC on +264 61 203 2406.

Table 2: Roche Product and contact details of Tyrosine kinase inhibitor (TKIs)

COMPANY	PRODUCT	ACTIVE INGREDIENT	REGISTRATION NUMBER	CONTACT DETAILS
Roche Products (Pty) Ltd	TARCEVA® 100 mg tablets TARCEVA® 150 mg tablets	Erlotinib Erlotinib	19/26/0060 19/26/0061	**Tel:** +2711 502 5000/5183 **Fax:** +27 11 268 5748 **E-mail:** south_africa.drugsafety@roche.com illovo.regulatory_affairs@roche.com

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