Pharmacovigilance

Adverse Event Report

Individual Case Safety Report (ICSR)

Report No.
MPN-AE-2024-00847

Report Date
15 September 2024

Classification
SERIOUS – EXPEDITED

Section 1 | Administrative Information

Reporting Organisation
Meridian Pharmaceutical Ltd.

Department
Global Drug Safety & Pharmacovigilance

Address
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London EC2N 4AA, United Kingdom

EudraVigilance Registration No.
EVMPD-GB-MPN-0041

Primary Contact – Safety Officer
Dr. Helena Strauss, PharmD

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Regulatory Submission Deadline
22 September 2024 (!) Expedited 7-Day

Worldwide Unique Case ID
GB-MPN-2024-AE-847

Source Type: ☒ Spontaneous Report ☐ Literature ☐ Clinical Trial ☐ Regulatory Authority ☐ Health Professional

Section 2 | Patient Information

Patient Initials
R.K.T.

Date of Birth
12 March 1968

Age at Onset
56 years

Sex
Male

Weight
82 kg

Height
178 cm

BMI
25.9 kg/m^2

Ethnicity (self-reported)
Caucasian

Country of Occurrence
United Kingdom

Reporting Physician
Dr. Marcus Okafor

Institution
Nexabridge General Hospital

Specialty
Cardiology / Internal Medicine

Relevant Medical History & Pre-existing Conditions

Condition	ICD-10	Onset	Status
Type 2 Diabetes Mellitus	E11.9	2015	Ongoing
Essential Hypertension	I10	2012	Ongoing
Dyslipidaemia	E78.5	2018	Ongoing
Stable Angina Pectoris	I20.8	2021	Ongoing
Previous MI (inferior)	I21.1	Jan 2022	Resolved

Known Allergies & Intolerances

Substance	Reaction Type	Severity
Penicillin (all classes)	Anaphylaxis	Life-threatening
Sulfonamides	Maculopapular rash	Moderate

Section 3 | Suspect Drug(s)

Proprietary (Brand) Name
Vertidorin®

International Non-proprietary Name (INN)
ranoxadine fumarate

ATC Code
C01EB99

Pharmaceutical Form
Film-coated tablet, 500 mg

Route of Administration
Oral

MAH (Marketing Authorisation Holder)
Vertex Biosciences AG

Authorisation No. (EMA)
EU/1/19/1411/001

Lot / Batch Number
VBA-240610-R

Expiry Date
June 2026

Indication (prescribed for)
Chronic stable angina pectoris

Dose / Regimen	Start Date	Stop Date	Duration	Action Taken
500 mg twice daily	01 Jun 2024	07 Sep 2024	98 days	Drug withdrawn

Causality Assessment	
Was the drug withdrawn?	Yes
Did event abate after withdrawal (dechallenge)?	Yes
Was drug reintroduced (rechallenge)?	No
Did event recur on rechallenge?	N/A

Section 4 | Concomitant Medications

Drug Name (INN)	Dose	Frequency	Indication	Ongoing?
metformin	1000 mg	Twice daily	T2DM	Yes
atorvastatin	40 mg	Once daily (PM)	Dyslipidaemia	Yes
amlodipine	5 mg	Once daily	Hypertension	Yes
aspirin	75 mg	Once daily	Anti-platelet	Yes
bisoprolol	5 mg	Once daily	Angina / HTN	Yes
ezetimibe	10 mg	Once daily	Dyslipidaemia	Yes

Section 5 | Adverse Event Description

Event Onset Date
07 September 2024

Date Reported to Meridian
10 September 2024

Event Resolution Date
13 September 2024 (partial)

Event Outcome
Recovering / Resolving

MedDRA System Organ Class (SOC)
Cardiac disorders (10007541)

MedDRA Preferred Term (PT)
QT interval prolongation (10037695)

QT Interval Prolongation with Symptomatic Ventricular Tachycardia (Torsade de Pointes, TdP)

The patient presented to the Nexabridge General Hospital Emergency Department on 07 September 2024 at 21:34 with a 40-minute history of palpitations, near-syncope, and diaphoresis. A 12-lead ECG recorded on arrival demonstrated a corrected QT interval (QTc, Bazett) of **567 ms** and multiple runs of non-sustained polymorphic ventricular tachycardia consistent with Torsade de Pointes. Baseline QTc (pre-Vertidorin, June 2024) was documented at 432 ms. The patient was admitted to the Coronary Care Unit (CCU) and cardiac monitoring was initiated.

Additional Adverse Events (Secondary)

MedDRA PT	SOC	Onset	Severity	Serious?
Palpitations	Cardiac	07 Sep 2024	Severe	No
Presyncope	Nervous System	07 Sep 2024	Severe	No
Diaphoresis	Skin/SC Tissue	07 Sep 2024	Moderate	No
Hypokalaemia	Metabolism	08 Sep 2024	Moderate	No

Seriousness Criteria (ICH E2A)

☑ Hospitalisation / Prolonged hospitalisation ☐ Death ☐ Life-threatening
☐ Congenital anomaly / birth defect ☐ Disability / Incapacity ☑ Medically significant event

Section 6 | Clinical & Laboratory Findings

ECG Findings

Parameter	Baseline (Jun 2024)	On Event (07 Sep 2024)	Post-withdrawal (13 Sep 2024)
QTc interval (Bazett)	432 ms	**567 ms**	458 ms
PR interval	168 ms	172 ms	170 ms
QRS duration	92 ms	96 ms	94 ms
Heart rate	68 bpm	82 bpm	72 bpm
Rhythm	Sinus	**TdP (NSVT)**	Sinus

Key Laboratory Results

Test	Result	Reference	Units	Flag
Potassium (K^+)	3.1	3.5–5.0	mmol/L	**LOW**
Magnesium (Mg^{2+})	0.62	0.70–1.05	mmol/L	**LOW**
Sodium (Na^+)	139	136–145	mmol/L	Normal
Creatinine	98	62–106	μmol/L	Normal
eGFR	74	>60	mL/min/1.73m^2	Normal
ALT	32	7–56	U/L	Normal
Troponin I (hs)	18	<53	ng/L	Normal
CK-MB	4.2	0–6.0	μg/L	Normal
Ranoxadine plasma level	3840	750–2000	ng/mL	**ELEVATED**

Clinical Interpretation: The significantly elevated plasma ranoxadine fumarate level (3840 ng/mL; 1.9× upper therapeutic limit) in the context of concurrent hypokalaemia (3.1 mmol/L) and hypomagnesaemia (0.62 mmol/L) is consistent with drug-induced QT prolongation precipitating Torsade de Pointes. Interaction with atorvastatin via CYP3A4 competitive inhibition is under investigation by the Clinical Pharmacology team.

Section 7 | Treatment & Clinical Management

1. **Immediate withdrawal** of Vertidorin® (ranoxadine fumarate) on 07 September 2024 at 22:10.
2. **Intravenous magnesium sulphate** 2 g over 15 minutes administered at 22:20; second dose 2 g administered at 23:05.
3. **Intravenous potassium chloride** 40 mmol in 0.9% NaCl over 4 hours to correct hypokalaemia.
4. Continuous **cardiac monitoring** and telemetry for 72 hours in CCU. No further TdP episodes recorded after 23:30 on 07 September 2024.
5. **12-lead ECG** performed every 8 hours; QTc demonstrated gradual shortening to 458 ms by 13 September 2024.
6. **Electrolyte supplementation** continued orally upon discharge; target K^+ > 4.5 mmol/L and Mg^{2+} > 0.85 mmol/L.
7. Alternative anti-anginal therapy initiated: **isosorbide mononitrate** 30 mg once daily.
8. Cardiology follow-up scheduled for **27 September 2024** with repeat ECG and electrolyte panel.

Section 8 | Causality Assessment

Method	Assessment	Rationale Summary
WHO-UMC Scale	**Probable**	Reasonable time sequence; known pharmacology; dechallenge positive; no alternative cause
Naranjo Algorithm	**Score 8 (Probable)**	Previous reports, positive dechallenge, plasma level confirms supratherapeutic exposure
Reporting Physician (Dr. Okafor)	**Related**	Clinical presentation consistent with ranoxadine-induced QT prolongation
Meridian Drug Safety Review	**Probable**	Confirmed by clinical pharmacology; batch recall not indicated; individual susceptibility factors present

Expectedness Assessment (per current SmPC Section 4.8)

☒ Unexpected (not listed as ADR in current Vertidorin® SmPC – Section 4.8 Revision 5, January 2024)
☐ Expected / Listed

Section 9 | Risk Evaluation & Regulatory Action

Signal Detection Status
New Safety Signal – Confirmed

Signal Category
Drug-induced QT prolongation / TdP

RMP (Risk Management Plan) Impact
Update Required – Module SV.5

Regulatory Submissions Required
MHRA (UK): 7-Day Expedited Report
EMA/EudraVigilance: 15-Day Expedited Report
FDA MedWatch (IND): 15-Day ICSR

SmPC / PIL Update Required?
Yes – Safety Variation submission Q4 2024

Action Item	Responsible Party / Deadline
Submit 7-day expedited ICSR to MHRA	Global Drug Safety Team / 22 Sep 2024
Submit to EudraVigilance	EU Regulatory Affairs / 25 Sep 2024
PSUR update to include this case	PSUR Manager / next PSUR due 31 Oct 2024
CYP3A4 interaction study initiation	Clinical Pharmacology / 30 Oct 2024
SmPC Section 4.4 / 4.8 amendment draft	Medical Writing / 15 Nov 2024
DHPC (Dear HCP Letter) assessment	Medical Affairs / 30 Nov 2024
Signal Closure Report	Safety Surveillance / 31 Dec 2024

Section 10 | Case Narrative Summary

This is a case of a **56-year-old male** (initials R.K.T.) with a background of Type 2 Diabetes Mellitus, Essential Hypertension, Dyslipidaemia, and Stable Angina Pectoris, who was commenced on Vertidorin® (ranoxadine fumarate 500 mg twice daily) in June 2024 for chronic stable angina.

On **07 September 2024**, approximately 98 days after initiation of therapy, the patient presented to the Emergency Department with acute onset palpitations, presyncope, and diaphoresis. ECG revealed a markedly prolonged QTc of 567 ms (baseline 432 ms) with non-sustained polymorphic ventricular tachycardia consistent with Torsade de Pointes. Critically, plasma ranoxadine fumarate levels were measured at 3840 ng/mL (reference therapeutic range 750–2000 ng/mL), indicating supratherapeutic drug exposure. Concurrent electrolyte abnormalities (hypokalaemia: 3.1 mmol/L; hypomagnesaemia: 0.62 mmol/L) are considered to have potentiated the arrhythmogenic risk. A drug-drug interaction via CYP3A4 competitive inhibition with atorvastatin is considered a probable contributing mechanism.

The patient was admitted to the Coronary Care Unit and treated successfully with intravenous magnesium sulphate (4 g total) and potassium chloride replacement. Vertidorin® was withdrawn, with subsequent resolution of TdP and progressive normalisation of QTc to 458 ms over six days.

Causality: Probable (WHO-UMC); Naranjo Score 8 (Probable). This event is assessed as **Unexpected** under the current Vertidorin® SmPC (v5, January 2024) and constitutes a **new safety signal** requiring SmPC amendment, RMP update, and expedited regulatory reporting.

Section 11 | Signatures & Certification

Reporting Safety Officer

Dr. Helena Strauss, PharmD

Title
Head of Global Drug Safety, Meridian Pharmaceutical Ltd.

Date
15 September 2024

Signature

Qualified Person for Pharmacovigilance (QPPV)

Prof. Sophie Langford, MD, MSc

EudraVigilance QPPV ID
EVQPPV-GB-MPN-001

Date
15 September 2024

Signature

Certification: I certify that to the best of my knowledge the information provided in this Individual Case Safety Report is accurate, complete, and has been prepared in accordance with ICH E2A guidelines, EMA Good Pharmacovigilance Practices (GVP Module VI), and applicable national legislation. This report is being submitted within the regulatory deadline applicable to serious, unexpected adverse drug reactions.

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drugsafety@meridian-pharma.fictional | *This document is CONFIDENTIAL and for Regulatory Purposes Only*

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