Medicines & Healthcare products
Regulatory Agency

MHRA

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17 June 2019

Dear Dr. Harris,

Prevent Future Deaths Report for Edward Hearn Date of Death (05.02.2018) (Case Ref: 00395-2018)

Thank you for copying to the MHRA your report dated 10 May 2019, under paragraph 7, schedule 5, of the Coroners and Justice Act 2009 and regulations 28 and 29 of the Coroners (Investigations) Regulations 2013, concerning the death of Mr Edward Hearn, who died on 5th February 2018 in King's College Hospital, (0395-18). This case report has been added to the MHRA's Yellow Card database of adverse drug reactions with the reference ADR 24406875.

Further to the information provided on this tragic case, and in accordance with your request, we have considered whether the statutory information currently provided by the marketing authorisation holder for prescribers (and patients) on the safe use of carfilzomib, is adequate, and whether any other regulatory measures could be taken to minimise the risk of cardiac arrest in subjects exposed to this drug. The statutory product information for cyclophosphamide and dexamethasone, used in combination with carfilzomib to treat Mr Hearn, was also considered. To this end, we have sought the advice of the Pharmacovigilance Expert Advisory Group (PEAG), an independent advisory group to the Commission on Human Medicines on matters of drug safety.

Information on the use of medicines is provided to healthcare professionals through the Summary of Product Characteristics (SmPC) and to patients through the Patient Information Leaflet (PIL). Full details of the SmPCs and PILs may be found on the MHRA's website (http://www.mhra.gov.uk/spc-pil/), and the electronic medicines compendium (https://www.medicines.org.uk/emc/).

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Carfilzomib (Kyprolis) in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Cyclophosphamide, a drug reported as comedication in the case of Mr. Hearn, is authorised for the treatment of a number of cancers, including multiple myeloma. The specific combination of carfilzomib, cyclophosphamide and dexamethasone is however not currently authorised outside of clinical trial use.

Section 4.4 (Special warnings and precautions for use) of the SmPC for carfilzomib states that new or worsening cardiac failure including fatal cases of myocardial ischaemia and infarction has occurred within a day following administration of the drug. The corresponding section for cyclophosphamide states that acute cardiac toxicity including severe QT prolongation has been reported with single doses as low as 20 mg/kg of cyclophosphamide. (please see Annex 1). The patient information leaflets of the two products include information which reflects the SmPC.

Therefore, on review of the available information, and in relation to actions within the remit of the MHRA, we are satisfied that the statutory SmPC and PIL for the medicines concerned in the case of Mr. Hearn currently provide relevant information to highlight the risk of serious cardiac disorders.

However, as we have reports of a total of 10 cases (including the case of Mr Hearn) of cardiac arrest, myocardial infarction or cardiac failure with carfilzomib, the PEAG has recommended that doctors prescribing the drug and cardiologists should be reminded of the requirements to monitor patients for cardiac disorders before and during treatment with carfilzomib. This information will be provided via an article in the MHRA's electronic bulletin for healthcare professionals, Drug Study Update, in the next 2-3 months. We will keep you informed.

Yours sincerely

[redacted]

[redacted]

Chief Executive
Medicines and Healthcare products Regulatory Agency

Annex 1

Section 4.4 (Special warnings and precautions for use)

Cardiac disorders

New or worsening cardiac failure (e.g. congestive cardiac failure, pulmonary oedema, decreased ejection fraction), myocardial ischaemia and infarction have occurred following administration of Kyprolis. Death due to cardiac arrest has occurred within a day of Kyprolis administration and fatal outcomes have been reported with cardiac failure and myocardial infarction.

While adequate hydration is required prior to dosing in cycle 1, all patients should be monitored for evidence of volume overload, especially patients at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in patients with baseline cardiac failure or who are at risk for cardiac failure (see section 4.2).

Stop Kyprolis for grade 3 or 4 cardiac events until recovery and consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment (see section 4.2).

The risk of cardiac failure is increased in elderly patients (≥ 75 years). The risk of cardiac failure is also increased in Asian patients.

Patients with New York Heart Association (NYHA) Class III and IV heart failure [moderate to severe], recent myocardial infarction, and conduction abnormalities uncontrolled by medicinal products were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications. Patients with signs or symptoms of NYHA Class III or IV cardiac failure, recent history of myocardial infarction (in the last 4 months), and in patients with uncontrolled angina or arrhythmias, should have a comprehensive medical assessment, prior to starting treatment with Kyprolis. This assessment should optimise the patient's status, with particular attention to blood pressure control and fluid management. Subsequently patients should be treated with caution and remain under close follow-up.

Electrocardiographic changes

There have been cases of QT interval prolongation reported in clinical studies. An effect of Kyprolis on QT interval cannot be excluded (see section 5.1).

Section 4.8 (Undesirable effects)

	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**
Cardiac disorders		Cardiac failure Myocardial infarction Atrial fibrillation	Cardiac arrest Myocardial ischaemia Pericarditis	

		Tachycardia Ejection fraction decreased Palpitations	Pericardial effusion	

Cyclophosphamide SmPC

Section 4.4 (Special warnings and precautions for use)

Cardiotoxicity, Use in Patients with Cardiac Disease

Myocarditis and myopericarditis, which may be accompanied by significant pericardial effusion and cardiac tamponade, have been reported with cyclophosphamide therapy and have led to severe, sometimes fatal congestive heart failure. Histopathologic examination has primarily shown hemorrhagic myocarditis. Haemopericardium has been reported secondary to hemorrhagic myocarditis and myocardial necrosis. Acute cardiac toxicity has been reported with single doses as low as 20 mg/kg of cyclophosphamide.

Following exposure to treatment regimens that included cyclophosphamide, supraventricular arrhythmias (including atrial fibrillation and flutter) as well as ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported in patients with and without other signs of cardiotoxicity.

The risk of cyclophosphamide cardiotoxicity as a result of treatment with cyclophosphamide may, for example, be increased following high doses of cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment of the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents. See section 4.5.

Particular caution is required in patients with risk factors for cardiotoxicity and in patients with a pre-existing cardiac disease.

Section 4.8 (undesirable effects)

	Very common (≥ 1/10)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare**	**Unknown**
Cardiac disorders			Cardiomyopathy Myocarditis Heart failure	Ventricular arrhythmia Supraventricular arrhythmia	Ventricular fibrillation Angina Myocardial infarction Pericarditis Atrial fibrillation	Ventricular tachycardia Cardiogenic shock Pericardial effusion Bradycardia Palpitations Electrocardiogram QT prolonged

Medicines & Healthcare products Regulatory Agency

MHRA

Andrew Harris
Coroner for Inner South District, Southwark Coroner's Court
1 Tennis Street, Southwark
SE1 1YD

Date 23/05/2019

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MHRA

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gov.uk/mhra

RECEIVED
05 JUN 2019

Dear Harris,

Local Identification Number:
Patient Initials: EH **Patient Age:** **Patient Sex:** Male
Yellow Card Reference Number: ADR 24406875

Thank you for reporting a suspected Adverse Drug Reaction, a copy is enclosed for your records.

If additional information becomes available about your patient you can email this to yellowcard@mhra.gov.uk, write to us at 'FREEPOST YELLOW CARD' or call our Yellow Card Information Service on 0808 100 3352 (10am to 2pm Monday-Friday). To help us link all correspondence, please quote the above Yellow Card reference number. Please remove patient personal identifiers such as name and date of birth from all information supplied, where possible.

All information is held in strict confidence and handled in line with our Yellow Card Privacy Policy, which can be found at https://yellowcard.mhra.gov.uk/privacy-policy/. If you wish to request a copy of the information we hold on your case or a copy of your report as it appears in our database, please write to us at the address above or email yellow.card@mhra.gov.uk citing your case reference number and details of your request.

You can find out more about the suspected Adverse Drug Reactions we have received at www.mhra.gov.uk/yellowcard.

Additionally, you can stay up-to-date on the latest advice for the safe use of medicines by reading our monthly bulletin Drug Safety Update, which is available on our website at www.gov.uk/drug-safety-update. You can receive a notification of each new bulletin by sending your email address to registration@mhradrugsafety.org.uk.

The Yellow Card Scheme is very important for early detection of previously unrecognised adverse effects and allows us to take appropriate action to improve the safe use of medicines. Your Yellow Card report is a valuable contribution to monitoring the safety of medicines in the UK.

Thank you again.

YellowCard
Helping to make medicines safer

MHRA

Report Overview - GB-MHRA-ESUSAR-203630347001-00101763

Suspect Reaction

Suspect Reactions Added	Outcome of the Reaction	Start Date	End Date
Cardiac arrest	fatal	03/02/2018	05/02/2018
Bronchopneumonia, organism unspecified	fatal	2018	-
Sepsis	fatal	2018	-

Do you consider the reaction to be serious?
Yes

Reaction severity
Patient died due to reaction,

Date of death
05/02/2018

Suspect Drug

Medicine	Brand	Batch No.	Start Date	End Date	Dosage	Indication	Action taken for reaction	Method	Source
Carfilzomib	Carfilzomib	-	22/01/2018	02/02/2018	-	Multiple myeloma	Drug withdrawn		-
CYCLOPHOSPHAMIDE	CYCLOPHOSPHAMIDE	-	22/01/2018	01/02/2018	-	Multiple myeloma	Drug withdrawn		-
DEXAMETHASONE	DEXAMETHASONE	-	22/01/2018	01/02/2018	-	Multiple myeloma	Drug withdrawn		-

Additional information
Trial Name: Cardamon - Carfilzomib/Cyclophosphamide/Dexamethasone with maintenance carfilzomib in untreated transplant-eligible patients with symptomatic MM to evaluate the benefit of upfront ASCT. Patient number: CAR-181 receiving treatment for Symptomatic Multiple Myeloma on the aforementioned clinical trial. CAR-181 was in the induction phase of the trial. The IMPs in induction are carfilzomib, cyclophosphamide and dexamethasone. In the induction phase of the trial, the patient receives cyclical treatment, with carfilzomib being given on day 1, 2, 8, 9, 15 and 16 over a 28 day cycle. Patients receive cyclophosphamide and dexamethasone on day 1, 8 and 15 of each cycle. The patient started cycle 1 on 22/01/2018 receiving all IMPs as per protocol. The patient had completed a delayed day 9 of cycle 1 on 02/02/2018 when he experienced the reaction. The patient was an in-patient being managed conservatively for a fracture of the hip sustained on 29/01/2018 due to a fall. Patient received cycle 1 day 8 on 01/02/2018 and day 9 on 02/02/2018. The patient was treated for a fever on 02/02/2018. On 03/02/2018 the patient experienced 2 asystolic cardiac arrests. The patient was admitted to ITU where upon return of spontaneous circulation on 04/02/2018 they had fixed dilated pupils. EEG performed on 05/02/2018 showed no consistent cortical activity in keeping with severe hypoxic encephalopathy. Death confirmed 17:00 05/02/2018. The patient had no previous cardiac history and recent ECHO and cardiac MRI were both normal. The report was received by the Sponsor on 05/02/2018. Cardiac arrest was assessed as related by the site investigator to carfilzomib and was assessed by the Sponsor as unexpected for carfilzomib hence meeting the definition of a 7 day SUSAR to carfilzomib. The trial Clinical Reviewer concurs with the site investigator that cardiac arrest is causally related to carfilzomib. The clinical reviewer also assessed cardiac arrest as related to cyclophosphamide. Therefore as cardiac arrest was assessed as unexpected for cyclophosphamide by the Sponsor, the event also meets the definition of a 7 day SUSAR to cyclophosphamide. The event of cardiac arrest was assessed as fatal on 05/02/2018. The results of a post-mortem are currently outstanding. UPDATE 19/11/2018 The treating site now have access to the coroner's report which states cause of death as 1a) bacterial bronchopneumonia, 1b) left ventricular hypertrophy and 1c) myeloma. As a result of the coroner's report's findings 'infection - bacterial bronchopneumonia' and 'sepsis' reactions have been added to the SUSAR report. Bronchopneumonia (fatal) was assessed as related by the site investigator to carfilzomib, cyclophosphamide and dexamethasone. Bronchopneumonia (fatal) was assessed by the Sponsor as unexpected for carfilzomib and dexamethasone and expected for cyclophosphamide hence meeting the definition of a SUSAR to carfilzomib and dexamethasone. Sepsis (fatal) was assessed as related by the site investigator to carfilzomib, cyclophosphamide and dexamethasone and was assessed by the Sponsor as unexpected for carfilzomib, cyclophosphamide and dexamethasone hence meeting the definition of a SUSAR to carfilzomib, cyclophosphamide and dexamethasone. The trial Clinical Reviewer concurs with the site investigator that bronchopneumonia (fatal) and sepsis (fatal) are causally related to carfilzomib, cyclophosphamide and dexamethasone.

Medicines & Healthcare products Regulatory Agency

MHRA

Yours sincerely,

[redacted]

[redacted]
Director
Vigilance and Risk Management of Medicines

Yellow Card

Submit Yellow Cards and view further information online at www.mhra.gov.uk/yellowcard

Download the Yellow Card App for free now.
Available on iOS and Android