SPONSOR:

Hospira UK Limited
Queensway
Leamington Spa, UK
Tel: +44 1926 820820
Fax: +44 1926 834445

Address changing during 2015 to:
Hospira UK Limited
Horizon, Honey Lane
Hurley, Maidenhead SL6 6RJ, UK
Tel: +44 1628 515 500
Fax: +44 1628 824 776

MARKETING AUTHORISATION HOLDER:

Hospira UK Limited
Queensway
Leamington Spa, UK
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Address changing during 2015 to:
Hospira UK Limited
Horizon, Honey Lane
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Post-Authorisation Safety Cohort Observation of Retacrit™ (epoetin zeta) Administered Subcutaneously for the Treatment of Renal Anaemia (PASCO II)

OBSERVATION PROTOCOL

Final Protocol Date:	**30 March 2010, Protocol Version 1.0**
Amendment 1 Date:	**05 August 2010, Protocol Version 2.0**
Amendment 2 Date:	**05 March 2012, Protocol Version 3.0**
Amendment 3 Date:	**20 March 2015, Protocol Version 4.0**
Project number	**EPOE-09-11**

1 SIGNATURES AND RESPONSIBILITIES

SPONSOR PROJECT MANAGER

_____ , 31 MAR 2015

Amy E. Potthoff, Date

Vice President, Medical Operations

SPONSOR DRUG SAFETY & EU QPPV FOR RETACRIT™

_____ , _____

Sam Owiredu-Yeboa, MB ChB, MSc, MBA Date

EEA QPPV, Head of Global Product Safety, Head Global Affiliate Relations

GLOBAL MEDICAL DIRECTOR & MEDICAL MONITOR

_____ , 31 MAR 2015

Seema Kumbhat, MD Date

Global Medical Director - Biologics

EMEA MEDICAL DIRECTOR

_____ , _____

Paul Audhya, MD, MBA Date

Vice President, Medical Affairs - EMEA

BIOSTATISTICS

_____ , 31 MAR 2015

Wayne Wisemandle, MA, Date

Head, Data Sciences, Global Clinical Development

1 SIGNATURES AND RESPONSIBILITIES

SPONSOR PROJECT MANAGER

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Head, Data Sciences, Global Clinical Development

GLOBAL PROTOCOL AMENDMENT 3: SUMMARY OF CHANGES

The purpose of this protocol amendment is to document the upcoming change of address of Hospira UK Ltd as study sponsor and MAH. In addition, this amendment also implements the following changes to the protocol:

- Addition of requirement to report occurrences of overdose and treatment error in order to comply with current guidance.
- Changes to sections relevant to safety reporting and guidance in order to be consistent with current guidances and practice.
- Removal of the Retacrit™ summary of product characteristics (SmPC) as an appendix in order to avoid unnecessary protocol amendments, if the SmPC is updated, in the future.
- Clarification of wording of selection criteria regarding expected availability of patients for observation for 3 years.

See Appendix 1, Global Protocol Amendment 3: List of changes for an itemized list of all text changes made to Protocol v3.0 (dated 05 March 2012) with section references.

2 ABSTRACT AND FLOW CHART

2.1 Abstract

NAME OF SPONSOR:	NAME OF FINISHED PRODUCT:	NAME OF ACTIVE INGREDIENTS:
Hospira UK Limited	Retacrit™	Epoetin zeta
TITLE	Post-Authorisation Safety Cohort Observation of Retacrit™ (epoetin zeta) Administered Subcutaneously for the Treatment of Renal Anaemia (PASCO II)	
PRIMARY OBJECTIVE	To estimate the incidence of Pure Red Cell Aplasia (PRCA), neutralising antibodies, lack of efficacy, and thromboembolic events under treatment with Retacrit™ (epoetin zeta) administered subcutaneously (SC) in patients with renal anaemia	
SECONDARY OBJECTIVE	To obtain information on adverse drug reactions (ADR) associated with Retacrit™ (epoetin zeta), use of epoetin zeta during pregnancy and lactation and data on long term use	
OBSERVATION DESIGN	Non-interventional, longitudinal, multi-centre, defined population, prospective observation	
PLANNED SAMPLE SIZE	6700 patients	
OBSERVATION CENTRES	Centres treating patients with renal disease and dialysis centres	
PATIENT SELECTION CRITERIA	Patients are eligible for enrolment if the following applies: – Patients currently under treatment with Retacrit™ (epoetin zeta) administered SC for renal anaemia – Informed consent given in writing after being provided with detailed information about the characteristics of this observation by the physician – Patients expected to be available for 3 years of observation Patients are <u>not eligible</u> for enrolment if the following applies: – Any contraindications as per the current SmPC of Retacrit™	
FORMULATION	According to the current SmPC of Retacrit™	
DOSAGE	Dosage as medically required for the treatment of the individual patient as determined by the patients' healthcare professional.	
ROUTE OF ADMINISTRATION	Only patients who are currently under SC treatment should be included in the observation.	
DURATION OF OBSERVATION	Up to 3 years observation for each patient will be documented	

NAME OF SPONSOR:	NAME OF FINISHED PRODUCT:	NAME OF ACTIVE INGREDIENTS:
Hospira UK Limited	Retacrit™	Epoetin zeta
PRIMARY ENDPOINTS	Incidence rate of adverse events of special interest - Pure red cell aplasia - Neutralising antibodies - Lack of efficacy - Thromboembolic events including cerebrovascular events (e.g. cerebrovascular accident, cerebral infarction, cerebral haemorrhage, transient ischaemic attack), deep vein thrombosis, myocardial infarction, and pulmonary embolism.	
SECONDARY ENDPOINTS	Descriptive evaluation including incidence rates of ADRs, pregnancy/lactation exposure and long term use	
PROCEDURE	This is a non-interventional, multi-centre, longitudinal observation with a defined population using a prospective cohort design. All steps related to the selection and enrolment of patients and the treatment of these patients will be in accordance with standard medical care. The decision to treat a patient will be independent of the decision to enrol a patient. All participating physicians will be asked if blood samples obtained from routine laboratory determinations **before** start of treatment with Retacrit™ (pre-dose serum sample) are available. Such samples would be centrally stored and, if necessary, analysed in a specialised laboratory for determination of neutralising antibodies. The following information will be collected per patient: - Pseudonymised patient identification - Demographic data - Medical history including selected risk factors - Exposure to erythropoiesis-stimulating agents (ESA) - Start of treatment with Retacrit™ - Adverse drug reactions - Adverse events of special interest - Pregnancy and lactation periods, if applicable	
STATISTICAL ANALYSIS	The incidence rate of adverse events of special interest will be calculated per patient. The ADRs will be evaluated and described including incidence rates.	

2.2 Flow Chart

Type of assessment planned	Entry examination	ongoing	Final examination
	Day 0		Week 156
Patient selection criteria	**X**	--	--
Informed consent	**X**	--	--
Pseudonymised patient identification	**X**	--	--
Demography	**X**	--	--
Exposure to ESA	**X**	--	--
Medical history	**X**	--	--
Retaining of blood samples for determination of neutralising antibodies	**X***	**X****	**X***
Occurrence of pregnancy/lactation	**X**	**X**	**X**
Adverse drug reactions	--	**X**	**X**
Adverse events of special interest (primary endpoints)	--	**X**	**X**

* if available
** if formation of antibodies is suspected or on request by the physician

3 TABLE OF CONTENTS

4 LIST OF ABBREVIATIONS AND TERMS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
CHMP	Committee for Medicinal Products for Human Use
cpm	Counts per minute
CRF	Case Report Form
CRO	Contract Research Organisation
EC	European Community
EDC	Electronic Data Capture
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
GVP	Good Pharmacovigilance Practice
HLT	High level term
MedDRA	Medical Dictionary for Regulatory Activities
PASCO	Post Authorisation Safety Cohort Observation
PRAC	Pharmacovigilance Risk Assessment Committee
PRCA	Pure red cell aplasia
PSUR	Periodic Safety Update Report
PT	Preferred term
RIP	Radio-immune-precipitation
rh-EPO	Recombinant human erythropoietin
RMP	Risk Management Plan
SC	subcutaneous
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard Operating Procedure
TC	Total amount of radioactive counts

5 ETHICAL AND LEGAL ASPECTS

This observation will be conducted in accordance with the following regulatory documents:

- Guideline on Good Pharmacovigilance Practices (GVP): Module VIII – Post Authorisation Safety Studies
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
- Applicable national legislation
- SOP system of the sponsor
- Applicable CRO SOPs

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

As required by GVP Module VIII on Post-Authorisation Safety Studies the study protocol will be submitted for review and approval by the relevant Institutional Review Board/Independent Ethics Committee.

5.2 Notification

For notification procedures to regulatory authorities or other bodies the applicable national legislation should be followed.

5.3 Patient Information/Informed Consent

Regarding the decision about therapy, there is no further information necessary which is beyond the physician's routine professional duty to inform the patient.

In this non-interventional study the physician is asked to provide, if available, remaining serum/plasma samples gained from routine laboratory determinations to a central specialised laboratory for the evaluation of the presence of anti-epoetin antibodies. In this case it is necessary to inform patients and/or their legal representatives of these potential additional lab tests and obtain written informed consent for the testing.

Participating patients and/or their legal representatives will be informed and asked for written informed consent regarding the collection and evaluation of data during the course of the non-interventional study.

The physician will ensure by written confirmation that informed consent was obtained and is available. The written confirmation and the informed consent will be archived by the physician.

6 INTRODUCTION

Erythropoietin is an essential growth factor required for production of red blood cells. The stimulus for erythropoietin production is believed to be the oxygen content of blood delivered to the renal interstitial cells. When the peritubular renal cells are functioning correctly, individuals with low haemoglobin concentrations will produce increased quantities of erythropoietin, resulting in increased red blood cell production (Ridley et al., 1994; Wang and Semenza, 1996; Lacombe and Mayeux, 1999).

Chronic renal failure is characterised by a progressive loss of kidney function resulting from inherited disorders or conditions such as diabetes mellitus or hypertension. In patients with chronic renal failure, deficiency of erythropoietin production is the primary cause of anaemia.

Information on indication, posology, contraindication interaction and side effects of Retacrit™ are specified in the current SmPC of Retacrit™.

7 OBSERVATION OBJECTIVE

The primary objective of the observation is to estimate the incidence of Pure Red Cell Aplasia (PRCA), neutralising antibodies, lack of efficacy and thromboembolic events under treatment with Retacrit™ (epoetin zeta) administered SC in patients with renal anaemia.

The secondary objective is to obtain information on ADR associated with Retacrit™ (epoetin zeta), use of epoetin zeta during pregnancy and lactation and data on long term use.

8 OBSERVATION PLAN

8.1 Overall Observation Design

The most important points regarding the design are the following:

- Non-interventional
- Longitudinal
- Multi-centre
- Defined population
- Prospective cohort observation
- Subcutaneous administration
- 6700 patients with renal anaemia
- Duration of observation: up to 3 years per patient

The observation will take place at centres treating patients with renal disease and dialysis centres.

8.2 Discussion of the Observation Design

Epoetin-associated PRCA is characterised by severe anaemia, low reticulocyte count, absence of erythroblasts, neutralising antibodies against erythropoietin and as a consequence nonresponse to therapeutically administered epoetin. Between 1999 and 2004, a total of 191 patients with epoetin-associated PRCA were identified in Australia, Canada, and certain countries of Europe and Asia, 95 percent of which were observed among haemodialysis patients who received several months SC a particular formulation of epoetin alfa that contained polysorbate 80 as stabiliser. Experience with the increase of PRCA between 1999 and 2004 identified SC use as risk factor and patients with renal anaemia as population at risk. Exposure-adjusted incidence rates peaked in 2002 at 4.5 per 10000 patient years (McKoy et al., 2008).

Changes of the formulation of that specific product as well as pharmacovigilance efforts and safety guidance resulted in a greater than 95 percent decrease in the number of new cases of epoetin-associated PRCA. Since then antibody-mediated PRCA is regarded as a rare class-related toxicity that occurs after extended periods of SC administration of epoetins to chronic renal failure patients with an incidence rate of 0.02 to 0.03 per 10000 patient years (McKoy et al., 2008).

The present post authorisation non-interventional observation, which is part of the marketing authorisation holder's post-approval commitment for further pharmacovigilance surveillance, is planned as a prospective cohort study enrolling patients with renal anaemia treated SC with epoetin zeta under routine conditions in a widespread use. A prospective cohort of 6700 patients will be followed up to 3 years treatment per patient with epoetin zeta.

The sample size was chosen accordingly to detect cases of epoetin-associated PRCA in order to demonstrate that the incidence rate under treatment with epoetin zeta is substantially below the risk observed between 1999 and 2004 and that it can be reasonably concluded that the incidence is in the range of the incidence of the class of ESA.

Although powered primarily to verify that no immunogenicity concern arises from the SC use of epoetin zeta, this observation will also be helpful due to its large sample size in providing further information about the incidence of thromboembolic events in patients with renal anaemia treated with ESAs.

8.3 Time Schedule

The overall time schedule for the observation is planned as follows:

- Start of observation: 2010
- Observation period per patient: up to 3 years
- Observation period PASCO II max. 8 years
- End of observation: 6700 patients completed the observation
- Final report: end of observation + 6 months

Safety interim data will be compiled and reported in the framework of PSUR and RMP submissions. Annual progress reports submitted to PRAC as per GVP Module VIII.

8.4 Participation of Healthcare Professionals

The decision to treat patients with Retacrit™ will be independent of the decision to enrol patients into the observation cohort. According to GVP Module VIII B.3 subject to the healthcare professional's terms of service, payment is restricted to compensation of the healthcare professional for any additional time and expenses incurred. No additional payment or inducement for a healthcare professional to participate in this post-authorisation safety observation is offered or given.

In order to avoid selection bias physicians participating in this observational cohort study should include patients, who are started on treatment with Retacrit™ and are willing to participate, consecutively.

8.5 Patient Selection Criteria

Patients are eligible for enrolment if the following applies:

- Patients treated SC with Retacrit™ (epoetin zeta) for renal anaemia.
- Informed consent given in writing after being provided with detailed information about the characteristics of this observation by the physician.
- Patients expected to be available for 3 years of observation.

Patients are not eligible for enrolment if the following applies:

- Any contraindication as per the current SmPC of Retacrit™.

8.6 Premature Discontinuation

Patients may withdraw at their own request without providing any reason. Decisions on treatment discontinuation or changes will be solely based on medical reasons, which are in the best interest of the patients. These decisions will be made independent of considerations of continuation in the observation. Patients who are discontinued from Retacrit™ treatment because of adverse events of special interest, or ADR, or pregnancy should be followed up until their medical condition is resolved or stabilised.

8.7 Treatment

8.7.1 Identity of Medication

Name of product:	Retacrit™
Active ingredient:	epoetin zeta
Mode of administration:	subcutaneous
Prescription status:	only available on prescription
Marketing authorisation holder:	Hospira UK Limited

For further information see current SmPC of Retacrit™.

8.7.2 Posology and Mode of Administration

Dosage as medically required for the treatment of the individual patient as determined by the patients' healthcare professional.

The initial Retacrit™ dosage will be documented in the patient record form (CRF) as total dosage per week and frequency of dose per week.

8.7.3 Duration of Treatment

The decision about the duration of treatment with Retacrit™ lies with the physician and is independent of his participation in this cohort observation. Within PASCO II the observation of treatment should be up to 3 years per patient.

8.7.4 Overdose and Medication Error

Any occurrence of overdose or medication error occurring during the study should be reported to Hospira EMEA Product Safety, using the prescribed form provided in the electronic data capture (EDC).

Overdose is defined as administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgment should always be applied.

Medication error is defined as an unintentional error in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer.

8.8 Safety Criteria

Primary endpoints:

Incidence rate of adverse events of special interest:

- Pure red cell aplasia
- Neutralising antibodies
- Lack of efficacy (as defined in the current SmPC)
- Thromboembolic events including cerebrovascular events (e.g. cerebrovascular accident, cerebral infarction, cerebral haemorrhage, transient ischaemic attack), deep vein thrombosis, myocardial infarction, and pulmonary embolism observed under treatment with Retacrit™ (epoetin zeta) administered SC in patients with renal anaemia.

Secondary endpoints:

Descriptive evaluation including incidence rates of ADRs.

Information on treatment with Retacrit™ (epoetin zeta)

- During pregnancy and lactation,
- On long term use.

8.8.1 Methods of Assessment of Data

All patient data assessed will be pseudonymised before transferred to the sponsor.

8.8.1.1 Primary Endpoints

Documentation of adverse events of special interest (AESI)

Adverse events of special interest (AESI) will be documented in the CRF and on a continuous basis on the following appropriate targeted AESI Report Forms

- Targeted Questionnaire for Thromboembolic events
- Targeted Questionnaire for Development of Neutralising Antibodies/Lack of Efficacy/PRCA

Reporting is independent of a causal relationship.
The following information will be documented on the AESI form:

- Diagnosis or main symptom
- Description of the course of the event
- Diagnostic test results to confirm diagnosis
- Pre-existing risk factors for development of the event and other relevant medical history
- Start date, end date or continuation of the event
- Outcome of the event
- Therapy of event
- Event seriousness
- Start date of Retacrit™ treatment, total weekly dose and date of last administration before event onset
- Causal relationship between Retacrit™ and the event
- Action taken with Retacrit™
- Performance of Retacrit™ re-administration and in case of re-administration recurrence of event
- Concomitant medication
- In case of fatal or life-threatening events: autopsy reports and/or hospital letters

For more detailed definition of AEs and description of the additional documentation and reporting procedures see Section 8.9.1 and 8.9.3, respectively.

Anti-epoetin antibodies

In suspicious cases with respective clinical symptoms for PRCA the sponsor has to be informed immediately (contact data see Section 8.9.3.1) and the blood samples of the respective patients will be analysed including, if available, blood samples (serum sample of at least 2 ml) from routine determinations **before** the start of treatment with Retacrit™ (pre-dose) and from the patient's final examination visit.

The analysis of antibodies against recombinant human erythropoietin (rh-EPO) in human serum samples is performed by radio-immune-precipitation (RIP) assay as described (Tacey et al. 2003). The RIP assay makes use of radioactive 125-iodinated rh-EPO which binds to circulating antibodies against rh-EPO in the serum of patients. This immune complex is precipitated by adding Protein G and the radioactive counts per minute (cpm) in the precipitate and measured by a gamma-counter. The percentage of counts per minute (%cpm) of the total amount of radioactive counts (TC) is calculated. Samples with %cpm >0.9% are considered positive, in the range between 0.3 and 0.9%cpm samples are borderline. Positive samples are diluted until this sample dilution becomes negative. The highest serum dilution with a result above 0.9%cpm is the final anti-EPO antibody result titration.

The central laboratory for the evaluation of antibodies will be:

IPM-GmbH Lademannbogen 6122339 Hamburg, Germany
Phone: +49-40-53805-514 Fax: +49-40-53805-854

Depending on the results of the RIP assay and the clinical symptoms of the patient further investigations, e.g. concerning the neutralising capacity of the antibodies, can be initiated.

8.8.1.2 Secondary Endpoints

Documentation of ADRs

Adverse drug reactions will be documented in the CRF and on a continuous basis on the AE/ADR Report Form. For more detailed definition of ADRs and description of the additional documentation and reporting procedures see Section 8.9.1 and 8.9.3, respectively. ADRs will be fully documented on the AE/ADR Report Form including the following:

- Diagnosis or main symptom
- Description of the course of the reaction, if needed
- Start date, end date or continuation of the reaction
- Outcome of the reaction
- Therapy of reaction
- Reaction seriousness
- Start date of Retacrit™ treatment, total weekly dose and date of last administration before reaction onset
- Causal relationship between Retacrit™ and ADR
- Action taken with Retacrit™
- Performance of Retacrit™ re-administration and in case of re-administration recurrence of reaction
- Concomitant medication and medical history
- In case of fatal or life-threatening events: autopsy reports and/or hospital letters

Documentation of Retacrit™ exposure during pregnancy and lactation

Retacrit™ exposure during pregnancy and lactation will be documented in the CRF and on a continuous basis on the Pregnancy/Lactation Report Form. For reporting procedures see Section 8.9.3. Retacrit™ induced ADR occurrence of the suckling during lactation will be followed up by routine pharmacovigilance. Pregnancies will be followed up until a final outcome is known. Live off-spring will be followed for at least 8 weeks after delivery.

8.8.1.3 Additional Data

Demographic data

At entry examination the physician documents the following data in the CRF:

- Pseudonymised patient identification (patient number)
- Date of birth
- Ethnic origin
- Gender
- Height
- Dry weight (weight measured post-dialysis in indoor clothing without shoes)
- First assessment of haemoglobin, haematocrit and vital signs (systolic and diastolic blood pressure and heart rate) in the week of the entry examination

- Availability of signed informed consent

Medical history: selected risk factors

At entry examination the following information will be documented in the CRF by tickboxes:

- Coronary heart disease
- Myocardial infarction
- Atrial fibrillation
- Other arterial or venous thrombotic or embolic events
- Peripheral arterial disease
- Cerebrovascular disease
- Transient cerebral ischaemic attack
- Stroke
- Thrombosis of deep vessels of lower extremities
- Pulmonary embolism
- Hyperlipidaemia
- Hypertension
- Diabetes (type 1/type 2, diabetic vascular complications yes/no)
- Heart failure (NYHA stage)
- Cancer (type of cancer, Date: since when)
- Smoking (current smoker, ex-smoker, never-smoker)

Medical history: other

At entry examination the following information will be documented in the CRF:

- Diagnosis leading to renal failure
- Date of first diagnosis of renal failure
- Other relevant medical history
- Date of first dialysis, average frequency of dialysis
- Date of first treatment with any ESA and average dose for the last 3 months.

Retacrit™ treatment

Following information will be documented in the CRF:

- First Retacrit™ treatment
- Retacrit™ dosage as total dosage per week and frequency of dosage per week in the week of the entry examination
- Route of administration
- Retacrit™ holidays

Premature termination

The reason for premature discontinuation of PASCO II participation will be documented in the CRF.

8.9 Assessment of Safety

8.9.1 Definitions

Adverse Events of Special Interest (AESI)

Adverse events of special interest are adverse medical occurrences, which have been determined by the sponsor as being important for the safety evaluation of Retacrit™. Adverse events of special interest are documented and recorded from the time when the patient has signed the informed consent until the end of the observation period, independently of causality assessments. For the purpose of this non-interventional study the following medical diagnoses fall under the definition of an adverse event of special interest:

- Pure red cell aplasia
- Neutralising antibodies
- Lack of efficacy
- Thromboembolic events including cerebrovascular events (e.g. cerebrovascular accident, cerebral infarction, cerebral haemorrhage, transient ischaemic attack), deep vein thrombosis, myocardial infarction, and pulmonary embolism

Adverse Reaction, Adverse Drug Reaction (ADR)

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Note: In the context of this observation the causality algorithm “certain”, “probable”, “possible”, “unlikely” and “not assessable” are considered a reasonable possibility of a causal relationship.

(Good Pharmacovigilance Practice Annex I - Definitions)

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the SmPC.

This includes class-related reactions which are mentioned in the SmPC but which are not specifically described as occurring with this product. For products authorised nationally, the relevant SmPC is that authorised by the competent authority in the Member State to whom the reaction is being reported.

For centrally authorised products, the relevant SmPC is the SmPC authorised by the European Commission. During the time period between a Committee for Medicinal Products for Human Use (CHMP) opinion in favour of granting a marketing authorisation and the Commission decision granting the marketing authorisation, the relevant SmPC is the SmPC annexed to the CHMP opinion.

(Good Pharmacovigilance Practice Annex I - Definitions)

Serious adverse reaction

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

(Good Pharmacovigilance Practice Annex I - Definitions)

8.9.2 Causality Assessment

The causal relationship between the adverse event and Retacrit™ will be assessed by the physician and the sponsor's responsible personnel according to the classification given below (Edwards et al. 1994). Adverse events which are assessed as certain, probably, possibly or unlikely related or which are not assessable will be considered as being related to Retacrit™.

Certain:

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possible:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely:

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

Not related:

- Event or laboratory test abnormality definitely not associated with the trial medication.

Not assessable:

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory.

8.9.3 Documentation and Reporting

8.9.3.1 Adverse Drug Reactions and Adverse Events of Special Interest

All ADRs and all AESI including any sign of lack of efficacy should be documented, in English, by the physician in the CRF and on the relevant AE/ADR or AESI Report Form. The completed AE/ADR or AESI Report Form will be forwarded within 24 hours of awareness of the event to:

EMEA Product Safety
Hospira UK Limited
Horizon, Honey Lane
Hurley, Maidenhead
SL6 6RJ, UK

Tel: +44 (0)1628 515 932
Mobile: +44 (0) 7812 369 961
Fax: +44 (0)1926 835 490
E-mail: DrugSafetyUK@hospira.com

Supporting information, e.g. hospital letter, laboratory results, should be sent by fax or e-mail, if available and necessary. In the case that the required information is not completely available, the physician should provide follow-up information via the AE/ADR or AESI Report Form within 24 hours of the additional information becoming available.

All serious ADRs and AESI will be followed up until a final outcome is known.

If deemed necessary, the sponsor may contact the physician in order to request additional information on the ADR/AESI. The physician must make every effort to obtain the additional information requested.

Serious ADRs and events of special interest will be reported to competent authorities according to the requirements of Regulation (EC) 726/2004.

8.9.3.2 Pregnancy and Lactation

Cases of pregnancy and lactation during treatment with Retacrit™ should be documented by the physician in the CRF and on the Pregnancy/Lactation Report Form. The Pregnancy/Lactation Report Form will be forwarded within 24 hours of becoming aware of the event to:

EMEA Product Safety
Hospira UK Limited
Horizon, Honey Lane
Hurley, Maidenhead
SL6 6RJ, UK

Tel: +44 (0)1628 515 932
Mobile: +44 (0) 7812 369 961
Fax: +44 (0)1926 835 490
E-mail: DrugSafetyUK@hospira.com

Pregnancies will be followed up until a final outcome is known. Live off-spring will be followed for at least 8 weeks after delivery.

9 DATA QUALITY ASSURANCE

9.1 Monitoring

Checks for plausibility and completeness will be performed automatically while entering data in the EDC system. Relevant missing information and discrepancies will be followed by queries.

The conduct of this observational cohort study will be supervised by designated monitors. A monitoring plan will describe scope, objective, responsibilities and procedures of monitoring.

Data checks will include:

- Confirmation of informed consent
- Documented AEs of special interest (primary endpoints)
- Documented ADRs
- Documented cases of pregnancy/lactation
- Confirmation that the patient is receiving SC Retacrit
- Documentation of serum samples and shipments (if applicable)

9.2 Data Handling

Data will be entered directly by the centres into the database (EDC) via electronic CRFs. An approval of the data by electronic signature is mandatory. During data entry, plausibility checks will be performed. If required paper CRFs will be made available for centres that do not have the capability of EDC. The data will be statistically evaluated and will be narrated in a final report.

Data handling will be performed according to national data protection laws.

10 BIOMETRICS AND STATISTICAL ASPECTS

10.1 General approach

All analyses will be specified in detail in a Statistical Analysis Plan (SAP). All data will be described appropriately.

10.2 Safety analysis

The primary endpoints in this cohort observation are PRCA, neutralising antibodies, lack of efficacy and thromboembolic events including cerebrovascular events (e.g. cerebrovascular accident, cerebral infarction, cerebral haemorrhage, transient ischaemic attack), deep vein thrombosis, myocardial infarction, and pulmonary embolism (documentation of adverse events of special interest; see section 8.8.1.1). Adverse drug reactions, pregnancy/lactation and long-term use are secondary endpoints.

In general it is recognised that most of the untoward medical occurrences (unfavourable and unintended signs, symptoms, or diseases) occurring in patients with renal failure can be explained by the poor underlying condition of the patients; most of these events are independent of the administration of epoetin zeta. There is often an under-reporting of these events, especially in case of no (double-blind) control treatment. In order to increase the quality of the recording and documentation of events potentially affected by epoetin zeta this project will focus on the recording of ADRs.

Patients can experience more than one ADR and the same ADR can occur more than once in the same patient. A single ADR report form may contain several events with the same ADR onset date. Multiple ADRs in the same patient are medically and consequently statistically dependent. Therefore, ADR rates should be calculated on patient counts.

The (crude) incidence rate is defined as the number of patients who experience a certain event (e.g. a specific Medical Dictionary for Regulatory Activities [MedDRA] Preferred Term), divided by the number of patients at risk. For the purpose of this cohort observation, a patient at risk is a patient who was exposed to epoetin zeta (i.e. epoetin zeta was applied at least once) after enrolment into PASCO II. The incidence rate will also be evaluated using the number of patient years exposed to epoetin zeta as the denominator.

The incidence rate is appropriate to describe the risk of an ADR if patients are observed for approximately the same period of time. Nevertheless, for a treatment and observation period of about three years the time pattern of occurrence is also of importance and the interpretation of the ADR profile should not be based on overall incidences only. At least for MedDRA Preferred Terms with an overall incidence of 0.05 or more the exact time pattern will therefore be displayed by cumulative ADR incidences derived from life-table analysis for 2-monthly intervals. The cumulative incidence accounts for the actual duration of follow-up as well as the time pattern of when the events occur relative to the number of patients at risk.

ADR incidences will be displayed by MedDRA primary System Organ Class (SOC), High Level Group Terms (HLGT), High Level Terms (HLT) and Preferred Term (PT).

In addition, 95% confidence limits will be calculated. If the number of ADR on the MedDRA PT level is 0 or 1, the 95% confidence intervals for crude rates will be derived from the continuity-corrected "score interval method" [Vollset, S.E. (1993): Confidence Intervals for a Binomial Proportion. Statistics in Medicine 12, 809 - 824] using the approach of Blyth and Still [Binomial Confidence Intervals. Journal of the American Statistical Association, 78, 108 - 116]. Confidence intervals for the cumulative adverse event incidence will be based on Greenwood's formula [Kalbfleisch, JD., Prentice, RL. (1980): The Statistical Analysis of Failure Time Data. John Wiley and Sons. New York]. It must be taken into account that the confidence limits have to be interpreted in an exploratory sense, not as exact statistical error probabilities.

The analyses will be restricted to those patients who receive epoetin zeta at least in part within PASCO II.

10.3 Sample Size considerations

As outlined in section 8.2the exposure-adjusted incidence of PRCA due to neutralising antibodies had a peak in 2002, with 4.5 per 10000 patient years; this corresponds to an incidence of 0.045% per patient year. Meanwhile antibody-mediated PRCA is regarded as a rare class-related toxicity that occurs after extended periods of SC administration of ESA to chronic renal failure patients, with an incidence of 0.02 to 0.03 per 10000 patient years; this corresponds to an incidence of 0.0002% to 0.0003% per patient year.

A prospective cohort will be followed up to 3 years treatment per patient with epoetin zeta. Alternatively one might consider observing more patients over a shorter period of time (e.g. 1 year) or fewer patients for even a longer period. The selected approach is regarded as a good compromise which takes into account that on the one hand side the risk of PRCA increases over time and that the number of available patients might be limited, and on the other side also allows generating sufficient data within a reasonable period.

The sample size was chosen to detect cases of epoetin-associated PRCA in order to demonstrate that the incidence rate under treatment with epoetin zeta is substantially below the incidence of 4.5 per 10000 patient years (this corresponds to an incidence of 0.135% within 3 years) observed in 2002.

With a sample size of 6700 patients those adverse events with a ‘true’ incidence of at least 0.00045 (i.e. 0.045%) within an observation period of 3 years (corresponding to an incidence of 0.00015 or 0.015% per patient year) will occur at least once with a probability of 0.95. If the incidence within 3 years is 0.00135 (0.135%) the probability to observe at least one event is 0.9999.

These calculations derive the probability to observe at least one event from an assumed (but actually not known) incidence. Based on the final results, the following calculations estimate the incidence and the corresponding confidence interval:

Incidence rate and confidence intervals, 6700 patients, observed number of events: 0, 1, 2, 3, 4 or 5

		2-sided 95% Confidence Interval (CI)		1-sided 95% CI
# Events	Incidence (in %)	Lower bound (in %)	Upper bound (in %)	Upper bound (in %)
0	0	0	0.0550	0.0447
1	0.0149	0.0004	0.0831	0.0708
2	0.0299	0.0036	0.1078	0.0939
3	0.0448	0.0092	0.1308	0.1157
4	0.0597	0.0163	0.1528	0.1366
5	0.0746	0.0242	0.1741	0.1568

For instance, if in this cohort observation 1 event occurs in 6700 patients, the observed incidence rate within the observation period of 3 years is 0.0149% and the resulting 95% confidence interval ranges from 0.0004% to 0.0831% (i.e. with 95% probability the true incidence lies within this estimated confidence interval).

Of the 6700 patients being recruited, 4,500 patients will be recruited by Hospira and the remainder coming from an identically designed trial with the same epoetin zeta.

11 FINAL REPORT AND ARCHIVING

11.1 Final Report

A fully integrated report will be prepared. The final report will be signed by all responsible functions mentioned in the present observation protocol.

11.2 Archiving

The marketing authorisation holder shall make arrangements for archiving of all study related material for future access and/or evaluations for at least 10 years. Safety-related material will be kept by the marketing authorisation holder for an unlimited time.

12 CONFIDENTIALITY AND PUBLICATION OF RESULTS

All information concerning the present observation is strictly confidential.

Any publication requires the written consent of the sponsor.

13 LITERATURE

Blyth and Still: Binomial Confidence Intervals. Journal of the American Statistical Association, 78, 108 – 116.

Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf. 1994, 10(2) 93 – 102.

Kalbfleisch, JD., Prentice, RL. (1980): The Statistical Analysis of Failure Time Data. John Wiley and Sons. New York.

Lacombe C, Mayeux P. Erythropoietin (Epo) receptor and Epo mimetics. Adv Nephrol Necker Hosp. 1999, 29 177 – 189.

McKoy JM, Stonecash RE, Cournoyer D, Rossert J, Nissenson AR, Raisch DW, Casadevall N, Bennett CL. Epoetin-associated pure red cell aplasia: past, present, and future considerations. Transfusion 2008; 48:1754-1762.

Ridley DM, Dawkins F, Perlin E. Erythropoietin: a review. J Natl Med Assoc. 1994; 86(2):129 - 35.

Tacey R, Greway A., Smiell J, Power D, Kromminga A, Daha M, Casadevall N, Kelley M. The detection of anti-erythropoietin antibodies in human serum and plasma. Part I. Validation of the protocol for a radioimmunoprecipitation assay. J Immunol Methods; 2003 Dec; 283(1-2):317-29.

Vollset, SE. (1993): Confidence Intervals for a Binomial Proportion. Statistics in Medicine 12, 809 - 824.

Wang GL, Semenza GL. Molecular basis of hypoxia-induced erythropoietin expression. Curr Opin Hematol. 1996, 3(2):156-62.

14 APPENDICES

Appendix 1 Global Protocol Amendment 3, Dated 20 Mar 2015: List of changes

The following specific changes have been made from protocol v3.0, dated 05 March 2012, in this global protocol amendment 3, dated 20 Mar 2015. Additions to the study protocol are shown in **bold** and deletions are shown in ~~strike through~~ text. Changes that were strictly editorial (e.g. updating formatting, correction of spelling errors) are not included. Changes to the Signature page are done to reflect the change in the signatories. All other changes are done to reflect the global protocol amendment.

Overview of Changes

Title Page

- Addition of Hospira UK Limited's New address in the Sponsor details
- Update of MAH details to Hospira UK limited, with a note to change in Hospira UK Limited's New address

SPONSOR:

Hospira UK Limited
Queensway
Leamington Spa, UK
Tel: +44 1926 820820
Fax: +44 1926 834445

Address changing during 2015 to:
Hospira UK Limited
Horizon, Honey Lane
Hurley, Maidenhead SL6 6RJ, UK
Tel: +44 1628 515 500
Fax: +44 1628 824 776

MARKETING AUTHORISATION HOLDER:

Hospira UK Limited
Queensway
Leamington Spa, UK
Tel: +44 1926 820820
Fax: +44 1926 834445

Address changing during 2015 to:
Hospira UK Limited
Horizon, Honey Lane
Hurley, Maidenhead SL6 6RJ, UK
Tel: +44 1628 515 500
Fax: +44 1628 824 776
~~**Hospira** Enterprises B.V.~~
~~Taurusavenue 19-21~~
~~NL-2132 LS Hoofdorp~~
~~Tel: +31 23 5560 100~~
~~Fax: +31 23 5560 180~~

- Version has been updated from 3.0 to 4.0

OBSERVATION PROTOCOL
~~(Incorporating Protocol Amendment 2, dated 05 March 2012)~~

Final Protocol Date: **30 March 2010, Protocol Version 1.0**

Amendment 1 Date: **05 August 2010, Protocol Version 2.0**

Amendment 2 Date: **05 March 2012, Protocol Version 3.0**

Amendment 3 Date: 20 March 2015, Protocol Version 4.0

Project number EPOE-09-11

Signature Page

- Signatory Authority (changed/updated the details of signatory authorities)

SPONSOR PROJECT MANAGER

_____ _____

~~Scott Treiber~~ **Amy E. Potthoff** Date

Vice President, ~~Global~~ Medical Operations ~~& Medical Affairs~~

SPONSOR DRUG SAFETY & EU QPPV FOR RETACRIT™

_____ _____

~~Philippa Guy~~ **Sam Owiredu-Yeboa, MB ChB, MSc, MBA**, Date

EEA QPPV, Head of **Global Product** Safety, **Head Global Affiliate Relations**

~~- Europe, Middle East and Africa~~

GLOBAL MEDICAL DIRECTOR & MEDICAL MONITOR

_____ , _____

Seema Kumbhat, MD **Date**

Global Medical Director - Biologics

EMEA MEDICAL DIRECTOR ~~ADVISOR FOR RETACRIT™~~

_____ _____

~~Kurt Gunter~~ **Paul Audhya, MD, MBA**, ~~Global Medical Director~~ Date

Vice President, ~~US~~**Medical Affairs - EMEA**

BIOSTATISTICS

_____ _____

~~Hyung-Woo Kim~~ **Wayne Wisemandle, MA,** Date

~~PhD, Assistant Director of Biostatistics~~ Date

Head Data Sciences, Global Clinical Development

Section 2.1 - Abstract

The following changes were done in section 2.1:

- Clarification of wording of selection criteria regarding expected availability of patients for observation for 3 years.
- Removed references made to Appendix 1 in the abstract for the points, “patient selection criteria” and “formulation”
- Added a row on the dosage information as shown below

PATIENT SELECTION CRITERIA	Patients are eligible for enrolment if the following applies: – Patients currently under treatment with Retacrit™ (epoetin zeta) administered ~~subcutaneously~~ **SC** for renal anaemia. – Informed consent given in writing after being provided with detailed information about the characteristics of this observation by the physician. – Patients expected to be available for ~~up to~~ 3 years of observation. Patients are <u>not eligible</u> for enrolment if the following applies: – Any contraindications as per the current SmPC ~~(section 4.3)~~ of Retacrit™ ~~- see Appendix 1~~
FORMULATION	According to the current SmPC of Retacrit™ ~~(section 2)~~ ~~see Appendix 1~~
DOSAGE	**Dosage as medically required for the treatment of the individual patient as determined by the patients' healthcare professional.**
ROUTE OF ADMINISTRATION	Only patients who are currently under SC treatment should be included in the observation ~~that are currently under subcutaneous treatment~~.

<u>Section 4 – List of abbreviations and terms</u>

Added/deleted the below mentioned terms in the list.

GVP	**Good Pharmacovigilance Practice**
~~**IEC**~~	~~Independent ethics committee~~
~~**IRB**~~	~~Institutional review board~~
PRAC	**Pharmacovigilance Risk Assessment Committee**
SmPC	Summary of product characteristics
~~**HLGT**~~	~~High level group terms~~

<u>Section – 5. ETHICAL AND LEGAL ASPECTS</u>

Reference to the regulatory document is changed

- ~~The Rules Governing Medicinal Products in the European Union – Volume 9A: Pharmacovigilance~~**Guideline on Good Pharmacovigilance Practices: Module VIII – Post Authorisation Safety Studies**

<u>Section – 5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)</u>

Reference to the regulatory document is changed

A**s required by GVP Module VIII on Post-Authorisation Safety Studies the study protocol will be submitted for review and approval by the relevant Institutional Review Board/Independent** ~~ccording to Volume 9A, Part I, chapter 7.7. "Ethical Issues" it is recom-~~

~~mended that non-interventional post-authorisation safety studies are referred to an~~ Ethics Committee.

Section 6 - Introduction

Removed references made to Appendix 1 and added the name of the medicinal product

Information on indication, posology, contraindication interaction and side effects of Retacrit™ are specified in the current SmPC ~~– see Appendix 1~~**of Retacrit**.

Section 8.3 – Time Schedule

Changed the text and reference to the guideline mentioned

Safety interim data will be compiled and reported in the framework of PSUR and RMP submissions. Annual progress reports submitted to ~~EMA~~ **PRAC** as per **GVP Module VIII**~~volume 9A.~~

Section - 8.4. Participation of Healthcare Professionals

Reference to the regulatory document is changed

The decision to treat patients with Retacrit™ will be independent of the decision to enrol patients into the observation cohort. According to~~ Volume 9A~~**GVP Module VIII B.3** subject to the healthcare professional's terms of service, payment is restricted to compensation of the healthcare professional for any additional time and expenses incurred. No additional payment or inducement for a healthcare professional to participate in this post-authorisation safety observation is offered or given.

Section 8.5 – Patient Selection Criteria

The following changes were made,

- Clarification of wording of selection criteria regarding expected availability of patients for observation for 3 years.
- Removed references made to Appendix 1

Patients are eligible for enrolment if the following applies:

- Patients treated ~~subcutaneously~~ **SC** with Retacrit™ (epoetin zeta) for renal anaemia.
- Informed consent given in writing after being provided with detailed information about the characteristics of this observation by the physician.
- Patients expected to be available for ~~up to~~ 3 years of observation.

Patients are not eligible for enrolment if the following applies:

- Any contraindication as per the current SmPC ~~(section 4.3)~~ of Retacrit™ ~~– see Appendix 1~~.

Section 8.7.1 – Identity of Medication

Corrected the name of the marketing authorization holder and removed references made to Appendix 1

Marketing authorisation holder:	Hospira UK Limited~~Enterprises B.V., Netherlands~~
~~Local representative:~~	~~Hospira UK Limited~~

For further information see current SmPC of Retacrit™ ~~(Appendix 1)~~.

Section - 8.7.4. Overdose and Medication Error

Added the section, to incorporate information pertaining to medication error and overdose as events to be reported, following an requirement to report cases of medication error or overdose

8.7.4 Overdose and Medication Error

Any occurrence of overdose or medication error occurring during the study should be reported to Hospira EMEA Product Safety, using the prescribed form provided in the EDC.

Overdose is defined as administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgment should always be applied.

Medication error is defined as an unintentional error in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer.

Section – 8.9.1. Definitions

Updated the product safety terminology/guidance references used in the section to be consistent with current guidances and SOPs

Adverse Reaction, Adverse Drug Reaction (ADR)

~~*A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.*~~

~~*Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility*~~

~~*Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).*~~

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Note: In the context of this observation the causality algorithm “certain”, “probable”, “possible”, “unlikely” and “not assessable” are considered a reasonable possibility of a causal relationship.

~~(The Rules Governing Medicinal Products in the European Union – Volume 9A: Pharmacovigilance~~**Good Pharmacovigilance Practice Annex I - Definitions**)

Unexpected adverse reaction

~~The marketing authorisation holder will assess all adverse drug reactions whether they are expected or unexpected according to the reference SPC using the following definition.~~

~~*An adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characteristics (SPC) (Article 1(13) of Directive 2001/83/EC)62.*~~

~~(The Rules Governing Medicinal Products in the European Union – Volume 9A: Pharmacovigilance)~~***An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.***

This includes class-related reactions which are mentioned in the summary of product characteristics (SmPC) but which are not specifically described as occurring with this product. For products authorised nationally, the relevant SmPC is that authorised by the competent authority in the Member State to whom the reaction is being reported.

For centrally authorised products, the relevant SmPC is the SmPC authorised by the European Commission. During the time period between a CHMP opinion in favour of granting a marketing authorisation and the Commission decision granting the marketing authorisation, the relevant SmPC is the SmPC annexed to the CHMP opinion.

(Good Pharmacovigilance Practice Annex I - Definitions)

Serious adverse reaction

~~*Serious adverse reaction means an adverse reaction which*~~

- ~~*results in death*~~
- ~~*is life-threatening*~~
- ~~*requires in-patient hospitalisation or prolongation of existing hospitalisation*~~
- ~~*results in persistent or significant disability or incapacity*~~
- ~~*or is a congenital anomaly/birth defect (Article 1(12) of Directive 2001/83/EC).*~~

~~*Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.*~~

~~*Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.*~~

~~*Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.*~~

~~(The Rules Governing Medicinal Products in the European Union – Volume 9A: Pharmacovigilance)~~ ***An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.***

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

(Good Pharmacovigilance Practice Annex I - Definitions)

Section – 8.9.3.1. Adverse Drug Reactions and Adverse Events of Special Interest

Made some editorial changes in the text of the section and added the new address of Hospira UK Limited in the table

All adverse drug reactions and all adverse events of special interest including any sign of lack of efficacy should be documented, in English, by the physician in the CRF and on the relevant AE/ADR or AESI Report Form. The completed AE/ADR or AESI Report Form will be forwarded **within 24hours of awareness of the event** to:

EMEA Product Safety
Hospira UK Limited
~~Queensway~~
~~Royal Leamington Spa~~
~~Warwickshire, CV31 3RW~~

~~Tel: +44 (0)1926 835279~~
~~Mobile: +44 (0)7860 469529Fax: +44 (0)1926 835490~~
Horizon, Honey Lane
Hurley, Maidenhead
SL6 6RJ, UK

Tel: +44 (0)1628 515 932
Mobile: +44 (0) 7812 369 961
Fax: +44 (0)1926 835 490
E-mail: DrugSafetyUK@hospira.com

~~within 24hrs of awareness of the event~~.

Supporting information, e.g. hospital letter, laboratory results, should be sent by fax **or e-mail**, if available and necessary. In the case that the required information is not completely available, the physician should provide follow-up information via the AE/ADR or AESI Report Form within 24 hours of the additional information becoming available.

Section – 8.9.3.2. Pregnancy and Lactation

Made some editorial changes in the text of the section and added the new address of Hospira UK Limited in the table

Cases of pregnancy and lactation during treatment with Retacrit™ should be documented by the physician in the CRF and on the Pregnancy/Lactation Report Form. The Pregnancy/Lactation Report Form will be forwarded **within 24hours of becoming aware of the event** to:

EMEA Product Safety
Hospira UK Limited
~~Queensway~~
~~Royal Leamington Spa~~
~~Warwickshire CV31 3RW~~

~~Tel: +44 (0)1926 835279~~
~~Mobile: +44 (0)7860 469529~~
~~Fax: +44 (0)1926 835490~~
Horizon, Honey Lane
Hurley, Maidenhead
SL6 6RJ, UK

Tel: +44 (0)1628 515 932
Mobile: +44 (0) 7812 369 961
Fax: +44 (0)1926 835 490
E-mail: DrugSafetyUK@hospira.com

~~within 24hrs of becoming aware of the event.~~

Pregnancies will be followed up until a final outcome is known. Live off-spring will be followed for at least 8 weeks after delivery.

Section – 9.1. Monitoring

Incorporated text in the section, to include information pertaining to data check references, which is consistent with practice and Project Management Plan

The conduct of this observational cohort study will be supervised by designated monitors. A monitoring plan will describe scope, objective, responsibilities and procedures of monitoring.

~~Source d~~**D**ata checks will ~~be performed for~~**include**:

- **C**~~c~~onfirmation of informed consent
- **D**~~d~~ocumented AEs of special interest (primary endpoints)
- **D**~~d~~ocumented ADRs
- **Documented cases of pregnancy/lactation**
- **Confirmation that the patient is receiving SC Retacrit**
- **Documentation of serum samples and shipments (if applicable)**

Section 14 - Appendices

Deleted the Appendix 1 – SmPC Retacrit™ to avoid unnecessary protocol amendments if the SmPC is updated in the future