CBG MEB

Public Assessment Report

Scientific discussion

Vasculocis 10 mg, kit for radiopharmaceutical preparation

(human serum albumin)

NL/H/3757/001/DC

Date: 28 February 2018

This module reflects the scientific discussion for the approval of Vasculocis 10 mg, kit for radiopharmaceutical preparation. The procedure was finalised on 2 August 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ERNV	Equilibrium Radionuclide Ventriculography
FPRNV	First-Pass Radionuclide Ventriculography
HSA	Human Serum Albumin
ICH	International Conference of Harmonisation
LV	Left Ventricle
LVEF	Left Ventricle Ejection Fraction
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RNV	Radionuclide Ventriculography
RV	Right Ventricle
RVEF	Right Ventricle Ejection Fraction
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SPECT	Single Photon Emission Computed Tomography
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vasculocis 10 mg, kit for radiopharmaceutical preparation, from CIS bio international (Gif sur Yvette).

After radiolabelling with sodium pertechnetate (99mTc) solution, the solution of technetium (99mTc) human albumin is indicated for planar radionuclide ventriculography (first-pass and equilibrium) and gated-SPECT scintigraphy of the cardiac chambers.

The product is for diagnostic use only.
A comprehensive description of the indications and posology is given in the SmPC

This decentralised procedure concerns a similar biological application. Vasculocis, registered in France by the same MAH CIS bio international since June 1988, is used as the reference product. The MAH CIS bio international (GIF sur Yvette) already has Marketing Authorisations for Vasculocis in France, Denmark, Finland and Sweden via national procedures with a full dossier. A statement is provided that Vasculocis is strictly identical to the reference product with respect to raw materials, composition, batch formula, manufacturing process, specifications, analytical procedures and packaging.

The marketing authorisation has been granted pursuant to Article 10(4) of Directive 2001/83/EC, a similar biological application

In general, it is possible to apply for a biosimilar product, provided that the reference product is authorised in accordance with Community acquis and that the data exclusivity period of the reference product has expired. For applications under article 10(4) of Directive 2001/83, the RMS can be a different member state than the RMS of the reference product/member state where the reference product is authorised. Also, for biosimilar applications, the legislation gives the opportunity to use a European Reference Product (ERP) when the reference product does not exist on a national market.

In view of the above, the RMS considered the type of procedure and legal basis chosen for this application acceptable.

In a biosimilar application the comparability with the reference product needs to be established. In this specific case, the product has the same manufacturing process as the reference medicinal product (Module 3 needs to be the same as for the reference product). Therefore, no additional non-clinical and clinical studies were considered necessary. However, the Clinical Overview had, similar to a generic application, to appropriately address the indications applied for based on recent references. As for any application, Module 3 of the application should be in line with current guidelines.

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

II. QUALITY ASPECTS

II.1 Introduction

Vasculocis is a kit for radiopharmaceutical preparation and is a white lyophilisate. Each 15 ml of product contains 10 mg of human serum albumin.

The kit for radiopharmaceutical preparation is packed in brown coloured, Type I, drawn glass vials, closed with chlorobutyl rubber stoppers and aluminium capsules.

The excipients are: stannous chloride dihydrate, hydrochloric acid and sodium chloride, under nitrogen atmosphere.

II.2 Drug Substance

The active substance is human albumin solution, an aqueous solution of protein obtained from plasma. It is a clear, slightly viscous liquid and almost colourless, yellow or green. Human albumin solution is described in the European Pharmacopoeia (Ph. Eur.).

The drug substance of Vasculocis is the drug product Vialebex 200 mg/L (human serum albumin – HSA), which is registered in France and Luxembourg. The active substance manufacturer (ASM) is responsible for the manufacturing and a quality agreement is in place.

Manufacturing process
The manufacturing process and its control are sufficiently described by the MAH. The process consists of pooling, filtration, filling, pasteurisation and incubation. The manufacturing process complies with Ph. Eur. requirements for albumin. No reprocessing was performed. The ASM will notify the MAH in case of changes to the manufacturing process and, if required, a variation to the dossier of Vasculocis will be submitted to the competent authorities accordingly.

Quality control of drug substance
Sufficient information is provided on starting materials. The information related to the human plasma used to manufacture the Drug Substance is provided to the MAH by the ASM and updated annually. The latest annual update, covering the year 2014, is included in the dossier. The delay in annual updates is accepted as it is sufficiently explained by the time needed for the national and MRP approval procedures, and because the information in the latest annual update gave no reason for concern.
All regional blood/plasma collection centres and test laboratories are regularly inspected by the French authorities. Blood centres associated with the regional centres operate within the same quality system and are authorised by the French authorities before starting operations. On-site inspection of these sites is based on the inspection strategy defined by the French authorities. Audits are performed by the ASM. Overall, the specification of the drug substance and test methods are in line with the monograph of the Ph. Eur.
Individual donations are tested for HBs antigen, HIV-1/2 antibodies and HCV antibodies. NAT testing for HCV, HIV-1, HBV, HAV and PB19 is performed on individual donations or minipools, and on the plasma-pool. In addition, the plasma-pool is tested for HBs antigen and HIV-1/2 antibodies. With the exception of the tests for HAV and PB19, all test kits used are CE-marked.
The epidemiological data give no reason for concern. Viral marker rates of the blood/plasma collection centres did not exceed alert limits in 2014 and no upward trends (2011-2014) are observed. The estimated overall residual risk of undetected infectious donations is low (1 per 3.81 million donations for HIV, 1 per 6.88 million donations for HCV, 1 per 5.78 million donations for HBV).

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Updated stability data covering the full shelf life are provided. All results comply with the specifications.

II.3 Medicinal Product

Pharmaceutical development
Vasculocis is a freeze-dried preparation of human serum albumin containing sodium chloride and stannous chloride dihydrate. The radionuclide is not part of the drug product.
The information provided on the pharmaceutical development is sufficient. The chosen formulation components, pharmaceutical form, container and labelling procedure are justified, and give no reason for concern. Stannous chloride dehydrate is used as reducing agent. Nitrogen is present to ensure an inert atmosphere and avoid oxidation of the tin. No changes have been introduced to the manufacturing process since the execution of the clinical and non-clinical studies.

Manufacturing process
The manufacturing process consists of 5 steps and has been validated according to relevant European guidelines. Briefly, the process consists of dialysis, bubbling, filtration, filling, freeze drying and sealing. No reprocessing is performed and no intermediates are defined. Process validation data on the product have been presented for 3 batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the Ph. Eur. or the British Pharmacopoeia (sodium chloride) requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form and are in line with the Ph. Eur. monograph. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three scale validation batches manufactured in 2013, 2014 and 2015, demonstrating compliance with the specification.

Stability of drug product
The shelf life of 12 months with the storage condition: “store the kit in a refrigerator (2 °C – 8 °C)” and the claimed 8 hour stability after labelling with the condition “do not store above 25 °C”, are supported by the provided stability data. With the exception of total tin content, all release tests were performed after 12 months of storage and specifications met. A stability study including assessment of albumin degradation/aggregation is ongoing. The MAH has committed to inform the authorities should any out of specification arise during the study.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

A statement is provided that the product subject of the present application is strictly identical to the reference product (Vasculocis registered in France) with respect to raw materials, composition, batch formula, manufacturing process, specifications, analytical procedures and packaging. The Quality documentation provided in Module 3 is sufficient. The application is acceptable from a quality point of view.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Human serum albumin is the main protein of human blood plasma and is exempted of ERA according to the Guideline.
Patients treated with Vasculocis may excrete 99m/99Tc (as pertechnate, TcO4-). However, considering that the frequency of dosing and the absolute dose of Tc is very low, and that the radioactive half-life of 99mTc is very short, it is anticipated that any environmental burden by Tc is extremely low and an environmental risk is only theoretical. Therefore, further ERA can be waived.

III.2 Discussion on the non-clinical aspects

The MAH provided a minimal description of non-clinical data. No new non-clinical data were presented. This could be defendable since HSA is a natural component of blood, no pharmacological effects are expected. However, more importantly, in biosimilar applications it is not the pharmacotoxicological characteristics per se that need to be determined, but the comparability with the reference product needs to be established. In this case the reference product is the same as the product applied for, which is marketed in France as Vasculocis 10 mg. Based on the quality assessment, it was established that this biosimilar product is in fact the same as the product already marketed. Therefore, further non-clinical data were waived.

IV. CLINICAL ASPECTS

IV.1 Introduction

Vasculocis is already used on the Dutch market for several years but "on doctors declaration" (artsenverklaring). The Dutch Healthcare Inspectorate (IGJ) has asked the company to apply for a marketing authorisation in the Netherlands. The reference product is already authorised in several EU countries including France, however there are differences in the therapeutic indication. In the CMDh position paper on processing of generic applications when the generic has more indications or fewer indications than the reference product in the CMS it is stated that for generic applications, according to Part II:2 of Annex 1 of Directive 2001/83/EC, clinical overviews should include an update of published literature relevant to the substance and the present application. Thus, the MAH has appropriately addressed the indication applied for in their clinical overview. Where the SmPC of the reference medicinal product was not harmonised across Member States, the MAH has reviewed the differences and highlighted these to the RMS.

IV.2 Pharmacokinetics

The information on clinical pharmacology is rather sparse. HSA is a naturally occurring component of blood. It remains within the blood stream for at least four hours. No significant concentration of technetium (99mTc) human serum albumin outside the vascular space is observed, except in excretory organs (kidney, bladder).

IV.3 Pharmacodynamics

Human albumin occurs in large amounts in the blood. A dose of Vasculocis represents only a small fraction of this amount. Therefore, no pharmacodynamic effects are expected. Also, pharmacodynamic effects are not observed.

IV.4 Clinical efficacy

Vasculocis is a biosimilar of the same product authorised in France. The efficacy of the product as assessed for the reference product from France has unfortunately not been available for review.
The MAH submitted no new studies. However, they provided a Clinical Overview with a review of published literature. The overview references 63 articles up to 2015.

According to the indication, after radiolabelling with sodium pertechnetate (99mTc) solution, the solution of technetium (99mTc) human albumin is indicated for planar radionuclide ventriculography (first-pass and equilibrium) and gated-SPECT scintigraphy of the cardiac chambers.

The most important radionuclide image acquisition techniques are:

- First-pass radionuclide ventriculography (FPRNV); a study comprises a short sequence of cardiac cycles acquired during the transit of a bolus through the heart. It provides high target to background ratio with temporal separation of the right ventricle (RV) and left ventricle (LV), but imaging is possible in only one projection.
- Equilibrium radionuclide ventriculography (planar ERNV); acquisition is performed with a gamma camera interfaced to a dedicated computer. Typical acquisitions should last at least 10–15 minutes.
- Tomographic radionuclide ventriculography (gated SPECT = Single Photon Emission Computed Tomography); the images are most commonly acquired with a two-headed gamma camera, collimator, energy window, orbit, matrix size and zoom similar to myocardial perfusion SPECT.

Left ventricle ejection fraction (LVEF) is by far the most important goal of all RNV techniques. Until recently, planar ERNV has been the modality most widely evaluated. First-pass study, planar equilibrium radionuclide ventriculography and tomographic equilibrium radionuclide ventriculography can all be acquired after only one injection of radiotracer.

Planar ERNV is not recommended for the evaluation of right ventricle ejection fraction (RVEF) because the activity present in the right atrium overlaps with the signal measured in the RV in the most common view. RV function can be, however, reliably assessed with tomographic acquisitions.

(99mTc)-HSA has been evaluated in several studies for the determination of LVEF. A good agreement for the measurement of LV volumes and LV ejection fraction exists between gated blood-pool tomography and gated myocardial perfusion tomography.

Radionuclide angiography has been used to study the effect of LV contractile performance on passive left atrial filling. A significant positive correlation between the LV peak ejection rate and left atria peak filling rate ($r=0.81$, $p<0.001$) was found, indicating that the left atria peak filling rate was strongly affected by the degree of LV peak ejection rate. This indicates that LV contractile performance plays an important role in determining left atria passive filling during ventricular systole.

Angio-scintigraphy is also a non-invasive technique for evaluation of the dynamic distribution of blood flow through the lung. Analysis of the pulmonary circulation system in terms of a distributed network of vessels of various lengths and diameters can best be conducted by characterising the transit time distribution of tracer particles through the system. A change in volume, a distension, or the opening of an extra vessel, a recruitment, will predictably result in a change in the transit time of the tracer in the corresponding section of the vascular bed and therefore modify the global transit time distribution.

A number of studies provide comparisons between various LVEF and RVEF measurement techniques. These are summarised in Table 1. In this table, lower reproducibility implies less variability and more accuracy.

Table 1: Comparison of the advantages, limitations and inter-operator reproducibility for measurements of LVEF and RVEF based on each imaging technique.

	Advantages	Limitations	Radiation	Reproducibility LVEF	Reproducibility RVEF	References
Invasive ventriculography	High 2D spatial resolution	Invasive Injection of iodinated contrast agent Radiation exposure	2-3 mSv	9-14 %		Hoffman [23]
Non-contrast-enhanced echocardiography	High availability Absence of radiation exposure Low cost	Difficult in case of poor echogenicity (e.g. obesity) or poor acoustic window (e.g. emphysema)	0 mSv	8-15 %	12 %	Hoffman [23] Chuang [7] Thomsoe [58] Thavendiranathan [57] Kjaergaard [31] Walker [62]
Contrast-enhanced echocardiography	High availability Absence of radiation exposure	Cost and side effects of echo contrast agents	0 mSv	4-10 %	12 %	Hoffman [23] Hundley [24] Thomsoe [58] Thavendiranathan [57] Kjaergaard [31]
3D-echocardiography	3D acquisition of the whole LV	Requires good echogenicity, acoustic window and dedicated echo probes	0 mSv	7-14 %	6 -12 %	Hoffman [23] Soliman [53] Sugeng [55] Thavendiranathan [57] Lu [36] Kjaergaard [31] Walker [62]

Radionuclide ventriculography (planar)	High robustness and reproducibility of measurements of LVEF	Radiation exposure Costs 2D imaging	4-8 mSv	2-3 %	Not recommended	Steyn [54] Dcou [10]
Radionuclide ventriculography (tomographic)	3D analysis of wall motion	Radiation exposure Costs	4-8 mSv	3-12 %	2-16 %	Dercle [12] Dcou [10] Odagiri [45] Jensen [28]
Gated myocardial perfusion scintigraphy	High robustness and reproducibility of measurements of LVEF	Less accurate in presence of myocardial infarction or high radiotracer uptake next to the heart (digestive or liver uptake) Evaluation of RV function not possible	1-8 mSv	2-4 %	Not feasible	Hiscock [22] Skrypniuk [52] Hijrs [18] Castell-Conesa [5] Steyn [54]
Gated cardiac CTA	High spatial resolution	High radiation exposure Injection of iodinated contrast agent Poor image quality in case of arrhythmia or breathing movement during the acquisition	12-18 mSv	2-12 %	2-3 %	Maffei [38] Sugeng [55] Delhaye [11]
Cardiac MRI	Absence of radiation exposure High tissular contrast High spatial resolution Quantification of myocardial mass	Complex monitoring in presence of CIED Degraded image quality in absence of good breath-hold or in presence of arrhythmia Claustrophobia Relatively long processing time Requires expertise in cardiac MRI acquisitions and image processing.	0 mSv	2-8 %	2-10%	Hoffman [22] Morton [42] Kiramitsos [29] Clarke [8] Mooij [41] Grothues [17] Sugeng [55] Walker [62]

IV.5 Clinical safety

Dosimetry

The radiation-absorbed doses to various organs after administration of (99mTc)-HSA are found in a publication from the International Commission on Radiological Protection, ICRP 53. The effective dose equivalent after administration of 800MBq is 6.32 mSv. The typical radiation-absorbed doses for an adult to the critical organs (adrenals, heart, kidneys, liver, lungs, and spleen) are 6.6, 16, 6.5, 5.8, 10.4, and 11.2mGy, respectively (please refer to Table 2 below).

Table 2: Absorbed doses per unit of administered activity

ORGAN	ABSORBED DOSE PER UNIT OF ADMINISTERED ACTIVITY (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	8.3E-03	1.0E-02	1.6E-02	2.5E-02	4.7E-02
Bladder wall	4.0E-03	5.8E-03	8.1E-03	1.1E-02	2.1E-02
Bone surfaces	8.9E-03	1.2E-02	2.2E-02	3.6E-02	7.1E-02
Breast	4.6E-03	4.7E-03	7.4E-03	1.1E-02	2.0E-02
Gastrointestinal tract					
Stomach wall	5.1E-03	6.5E-03	1.0E-02	1.4E-02	2.5E-02
Small intestine	4.8E-03	5.8E-03	8.8E-03	1.3E-02	2.4E-02
Upper large intestine wall	4.7E-03	6.0E-03	8.6E-03	1.4E-02	2.3E-02
Lower large intestine wall	4.2E-03	5.6E-03	8.6E-03	1.2E-02	2.3E-02
Heart	2.0E-02	2.5E-02	3.6E-02	5.4E-02	9.2E-02
Kidneys	8.1E-03	9.7E-03	1.5E-02	2.4E-02	4.4E-02
Liver	7.3E-03	8.7E-03	1.4E-02	2.1E-02	3.7E-02
Lungs	1.3E-02	1.6E-02	2.6E-02	4.1E-02	7.6E-02
Ovaries	4.4E-03	5.7E-03	8.5E-03	1.3E-02	2.3E-02
Pancreas	6.4E-03	7.7E-03	1.2E-02	1.7E-02	3.0E-02
Red marrow	7.5E-03	9.0E-03	1.3E-02	2.0E-02	3.5E-02
Spleen	1.4E-02	1.6E-02	2.6E-02	4.0E-02	7.6E-02
Testes	2.9E-03	3.9E-03	5.7E-03	8.8E-03	1.6E-02
Thyroid	4.9E-03	7.3E-03	1.2E-02	1.9E-02	3.5E-02
Uterus	4.8E-03	5.7E-03	8.5E-03	1.3E-02	2.3E-02
Other tissue	4.0E-03	4.7E-03	6.9E-03	1.1E-02	2.0E-02
Effective dose equivalent (mSv/MBq)	7.9E-03	9.7E-03	1.5E-02	2.3E-02	4.2E-02

Exposure

Vasculocis is currently authorised to be marketed in 5 countries worldwide. The first market launch was in 1986, in France, and since then extensive clinical experience has been collected. During this entire time, registration has never had to be withdrawn or suspended on the grounds of safety. The product is also marketed in 21 additional countries (in 3 under import license, in 17 under medical prescription, and in one country where there is no need of authorisation).

Since 30 April 1994 (earliest available sales data), it is estimated that between 619,800 and 826,400 patients received Vasculocis, most of them from the EU (please refer to Table 3 below).

Table 3: Cumulative exposure data from marketing experience for EU countries

Country	Number of exposed patients
Austria	2,070 – 2,760
Belgium	112,650 – 150,200
Croatia	930 – 1,240
Cyprus	105 – 140
Czech Republic	390 – 520
Denmark	80,835 – 107,780
Estonia	60 – 80
Finland	2,100 – 2,800
France	300,915 – 401,220
Germany	9,330 – 12,440
Greece	765 – 1,020
Ireland	30 – 40
Italy	870 – 1,160
Luxembourg	2,865 – 3,820
Netherlands	67,980 – 90,640
Norway	45 – 60
Poland	450 – 600
Romania	30 – 40
Spain	2,475 – 3,300
Sweden	7,635 – 10,180
United Kingdom	3,225 – 4,300
Total	595,755 – 794,340

Adverse events

The MAH submitted no new studies. However, they provided a Clinical Overview with a review of published literature. This was supplemented by the latest periodic safety update report which was the most useful source of adverse event information in the dossier.

The cumulative adverse reactions as reported to the MAH are shown below in Table 4. These data include spontaneous reports, including competent authorities (worldwide) and literature and non-interventional studies and reports from other solicited sources post-marketing.

Table 4: Cumulative summary tabulations of adverse reactions from post-marketing data sources.

SOC MedDRA PT	Serious			Non serious			Total
	Listed	UnListed	Total	Listed	UnListed	Total	
Nervous system disorders (10029205) [3]							
Dizziness			0	2		2	2
Dysgeusia			0		1	1	1
Headache			0		1	1	1
Eye disorders (10015919) [1]							
Eyelid oedema			0	1		1	1
Cardiac disorders (10007541) [1]							
Tachycardia			0	1		1	1
Vascular disorders (10047065) [1]							
Syncope			0		1	1	1
Gastrointestinal disorders (10017947) [2]							
Abdominal pain upper			0		1	1	1
Nausea			0		1	1	1
Skin and subcutaneous tissue disorders (10040785) [4]							
Erythema			0	2		2	2

Hyperhidrosis			0	2		2	2
Palmar erythema			0		1	1	1
Skin exfoliation			0	1		1	1
General disorders and administration site conditions (10018065) [9]							
Chest pain			0		1	1	1
Chills			0	1	1	2	2
Drug ineffective			0		3	3	3
Extravasation			0		1	1	1
Face oedema	1		1			0	1
Feeling hot			0		1	1	1
Local swelling			0		1	1	1
Malaise			0	2		2	2
Thirst			0		1	1	1
Investigations (10022891) [1]							
Radioisotope scan abnormal		1	1		21	21	22
Injury, poisoning and procedural complications (10022117) [2]							
Poor quality drug administered			0		5	5	5
Wrong technique in drug usage process			0		2	2	2
Surgical and medical procedures (10042613) [1]							
Off label use			0		1	1	1
TOTAL	1	1	2	12	44	56	58

Conclusion

The MAH provided no estimates based on adverse events rates in clinical trials. Based on post-marketing data, the rate of adverse events may be very low, as only 58 cases in >619,800 exposures were reported, or < 1/10,686 exposures. The listing of adverse events in the SmPC is acceptable.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Vasculocis.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity and anaphylactoid reactions, including their symptoms.
Important potential risks	- Cancer induction and hereditary defects - Transmission of an infectious agent via product
Missing information	- Drug exposure during pregnancy - Drug exposure during breast-feeding - Paediatric use (safety of Vasculocis in patients under the age of 18.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies for the reference product from France and longstanding clinical experience of human serum albumin. No new clinical studies were conducted. On the basis thereof, the efficacy of Vasculocis can be considered established and acceptable.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package

leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vasculocis 10 mg, kit for radiopharmaceutical preparation is considered a biosimilar of already authorised reference medicinal product Vasculocis registered in France. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise has been established.

In the Board meetings of 28 July 2016 and 10 May 2017, an issue has been discussed regarding available data concerning a starting material. The issue has been resolved.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Vasculocis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 August 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse