2 August 2012
EMA/518790/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cuprymina

International non-proprietary name: **Copper (^{64}Cu) chloride**

Procedure No. **EMEA/H/C/002136**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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List of abbreviations

^{64}Cu	Copper-64
$^{64}CuCl_2$	Copper (^{64}Cu) chloride
^{64}Ni	Nickel-64
^{64}Zn	Zinc-64
^{18}F	Fluorine-18
^{111}In	Indium-111
ATSM	Diacetyl bis(N4-methylthiosemicarbazone)
BFC	Bifunctional chelator
BSE	Bovine Spongiform Encephalopathy
C_{24}	Concentration at 24 hours
CA-9	carbonic anyhdrase IX
CB	Cross-bridged (macrocyclic chelators).
CBF	Cerebral blood flow
CB-TE2A	4,11-Bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane
CCO	cytochrome-c oxidase
CCS	copper chaperone Cu for SOD1
CET	Central European Time
CHD	Coronary heart disease
CHMP	Committee for Medicinal Products for Human use
CMRO2	metabolic rate of oxygen
COX-2	cyclo-oxygenase-2
CR	Complete Response
CT	Computer Tomography
DTPA	diethylenetriaminepentaacetic acid
DTPA-OC	diethylenetriaminepentaacetic acid-octreotide
D/E	delayed to early
DOTA	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTA-NHS	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid mono(hydroxy-succinimide ester)
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor
FDG	fluoro-2-deoxy-D-glucose
FDG-PET	18F- Positron emission tomography
GI	gastrointestinal
GIST	gastrointestinal stromal tumour
GLP	Good Laboratory Practices
HAMA	Human against mouse antibodies
IMRT	Intensity Modulated radiotherapy
keV/kV	kilo electron volt/ kilovolt
LAL	Limulus Amebocyte Lysate
LLI	lower large intestine
MAb	Monoclonal Antibody
MBq	MegaBecquerel
MeV/ MV	Mega electron volt/ megavolt
MRI	Magnetic Resonance Imaging
ND	not determined
NOEL	No observed effect level
NOAEL	no-observed-adverse-effect-level
NSCLC	non-small-cell lung cancer
OEF	oxygen extraction fraction
PET	Positron emission tomography

Ph. Eur.	European Pharmacopeia
PK	Pharmacokinetics
PTSM	Pyruvaldehyde bis(N4-methylthiosemicarbazone
PTDI	provisional tolerable daily intake
RDA	Recommended Daily Dose
RTK	receptor tyrosine kinases
SOD1	Superoxide dismutase [Cu-Zn] also known as superoxide dismutase 1 or SOD1
SmPC	Summary of Product Characteristics
SPECT	Single photon emission computed tomography
SSTr	somatostatin receptor
SUV	Standard uptake value
Sv	Sievert
TETA	1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetraacetic acid
TETA-OC	1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetraacetic acid-octeotride
TLC	Thin Layer Chromatography
T/M	tumour-to-muscle
TSE	Transmissible Spongiform Encephalopathy
ULI	Upper large intestine
UL	upper intake level
VEGF	vascular endothelial growth factor
Y3-TATE	Tyrosine3-octreotate = (D)Phe-cyclo[Cys-Tyr-(D)Trp-Lys-Thr-Cys]-Thr
WND	Wilson protein

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SPARKLE S.r.l submitted on 22 September 2010 an application for a Marketing Authorisation to the European Medicines Agency (EMA) for Cuprymina, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 September 2007.

The applicant applied for the following indication: Cuprymina is a radiopharmaceutical precursor. It is not intended for direct use in patients. This medicinal product must be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicant's own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/189/2010 on the granting of a product-specific waiver for all subsets of the paediatric population.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance Copper (^{64}cu) chloride contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 April 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Ian Hudson** Co-Rapporteur: **Daniela Melchiorri**

- The application was received by the EMA on 22 September 2010.
- The procedure started on 20 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2011 .
- During the meeting on 14-17 February 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 February 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 November 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 December 2011.
- During the CHMP meeting on 16-19 January 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 April 2012.
- During the meeting on 21-24 May 2012, the CHMP agreed that no oral explanation was needed.
- During the meeting on 18-21 June 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Cuprymina on 21 June 2012.

2. Scientific discussion

2.1. Introduction

Cuprymina contains ^{64}Cu, a radioisotope of copper, as Copper (^{64}Cu) chloride in solution and is intended for use as a radiopharmaceutical precursor for radiolabelling of carrier molecules that have been specifically developed and authorised for radiolabelling with this radionuclide. Cuprymina is not intended for direct administration to patient.

^{64}Cu has a half-life of 12.7 hours. ^{64}Cu decays by an emission of β^+ particles (17.6 %) with a maximum energy of 0.66 MeV, an emission of β^- particles (38.5 %) with a maximum energy of 0.58 MeV and electronic capture (43.9 %), that allows its use both as diagnostic radioisotope (β^+) and therapeutic radioisotope (β^- EC). The β+ and β- emissions (positrons and electrons) have a range of the order of 1 mm. In its decay, ^{64}Cu also emits 2 gamma rays at 511.0 KeV and 1345.77 KeV (1.35477 ±0.00016 MeV) with a high penetration power. The process of decay by electron capture is associated with emission of 2 high intensity Auger electrons, that release all their energy in a very short range (of the order of 6 µm), and have a high level of cytotoxicity on cells.

^{64}Cu decays in stable ^{64}Ni (61 %) by an emission of β^+ particles (18 %) or by an electronic capture (43 %). ^{64}Cu decays also in stable ^{64}Zn by emission of β^- particles (39 %).

The indication for Cuprymina is the following:

"Cuprymina is a radiopharmaceutical precursor. It is not intended for direct use in patients. This medicinal product must be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide."

Cuprymina is only to be used by specialists experienced with in vitro radiolabelling.

The quantity of Cuprymina required for radiolabelling and the quantity of ^{64}Cu-labelled medicinal product that is subsequently administered will depend on the medicinal product radiolabelled and its intended use.

2.2. Quality aspects

2.2.1. Introduction

Cuprymina is a radiopharmaceutical precursor solution of Copper (^{64}Cu) chloride, intended for the radio-labelling of carrier molecules which have been specifically developed and authorised for radio-labelling with copper. As such Cuprymina is not intended for direct administration to patients, but will be used to radio-label suitable carrier (ligand) molecules.

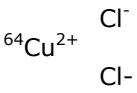
The product is supplied as a sterile and endotoxin-free solution in HCl and is presented in a 10 ml glass vial, containing 925 MBq/ml (corresponding to 0.25 micrograms of ^{64}Cu). The quantity of Cuprymina required for radiolabelling and the quantity of ^{64}Cu-labelled carrier molecules that is subsequently administered depend on the radiolabelled product and its intended use.

2.2.2. Active Substance

Copper (^{64}Cu) chloride is a radiopharmaceutical precursor. The active substance is not isolated during the manufacture and is dissolved in a solution of diluted hydrochloric acid. The general properties of

the active substance therefore relate to the active substance Copper (^{64}Cu) chloride in diluted hydrochloric acid solution.

The chemical structure of the Copper (^{64}Cu) Chloride is as follows:



Copper [^{64}Cu] has a characteristic decay scheme, with decay by three schemes:

- β^+ emission of 0.66 MeV (18 %) – diagnostic potential
- β^- emission of 0.58 MeV (38.5 %) – therapeutic potential
- Electron capture (43.5 %) – therapeutic potential

^{64}Cu has a half life $t_{1/2}$ of 12.7 hours. 3 mL of bulk solution contains from 9.25 to 55.55 GBq ^{64}Cu, corresponding to 2.5-15 micrograms of ^{64}Cu. The nominal specific activity is ≥ 3700 MBq ^{64}Cu /µg Copper at the expiry date and time (24 h from the End of Synthesis).

Manufacture

The copper (^{64}Cu) chloride active substance is prepared in a computer-assisted synthesizer unit. Its manufacture is based on a chemical process involving three steps:

1. Preparation of the target: electro-deposition of ^{64}Ni onto a gold disk.
2. Irradiation of the target: the electroplated ^{64}Ni disk is irradiated using a cyclotron to produce the ^{64}Cu.
3. Nuclide separation: dissolution of the electro-deposited ^{64}Cu in HCl 6N followed by radionuclidic purification through an ion exchange column. This step is carried out in a dedicated synthesis module by an automated process.

Radioactivity values are monitored and recorded throughout the synthesis process and these are summarised against time at the end of each synthesis. These measurements allow the yield at each step of the process to be determined and controlled.

Copper (^{64}Cu) chloride bulk solution is the active substance and it is never isolated in the automated process.

The manufacturing process is well described and appropriate in-process controls are in place. As the synthesis is continuous and automated and the radionuclide has a short half life and high radioactivity, no intermediates are isolated during the production of the bulk drug substance solution. Critical steps are therefore controlled by means of ensuring that processing parameters are consistent and controlled. Description and validation of the ICP-MS method used for testing the starting material ^{64}Ni was not considered sufficient and the issue was raised as a major objection in the D120 LoQ. The issue was not considered totally resolved at D180 and clarification was requested as a major objection. The applicant provided adequate responses to the remaining objection and the ICP-MS method is now considered acceptable. The starting materials are sufficiently characterised, with the specifications and testing procedures being acceptable.

Radionuclidic identification measurement using gamma spectroscopy is used to confirm the identification of the drug substance as Copper (^{64}Cu) chloride.

Impurities in the active substance are inorganic impurities that may be divided into radioisotopic impurities and metallic impurities. The radioisotopic impurities may arise from irradiation of isotopic impurities in the target material or from the irradiation of the target ^{64}Ni. These impurities are important because they may influence the radionuclidic purity of the drug substance. The metallic impurities may derive from the decay of radioactive impurities, of ^{64}Cu and of starting material.

Radionuclidic impurities and their physical characteristics have been adequately described in this section. Metallic impurities that may be present during the process have been described and are reported satisfactorily.

Specification

Since the bulk active substance cannot be isolated within the synthesis module, the activity control is the only check carried out and it is automatically measured at the end of the synthesis. However during the process development and characterisation studies carried out using a manual procedure, the main characteristics of the active substance were defined and are tested at the drug product level.

It is accepted that an official active substance specification does not exist for the active substance since the manufacturing process from starting material to drug product is continuous and the active substance is not isolated at any time. The in process controls are considered to control the process of active substance manufacture adequately.

The only procedure performed that is specific to the active substance is radioactivity measured at each of the three ionisation chamber detectors within the synthesis module. The radioactivity detector is calibrated to appropriate standards.

Stability

Although the active substance is not isolated, manual pilot scale batches were manufactured for which the following stability studies have been carried out:

- Testing at 25 °C±2 °C
- Stress Testing at 40 °C ±2 °C
- Stress Testing at 0 °C ±2 °C

These studies have been performed for 24 hours with testing intervals: T0, T8, T12, T16 and T24

The following parameters have been investigated:

- Radionuclidic identification
- Radionuclidic purity
- Radiochemical Purity
- Chemical purity
- Half Life

Sterility and bacterial endotoxin have not been tested, which is acceptable as the active substance is not isolated and the finished product is tested for sterility

The active substance characteristics remains within the limits for the tested parameters up to the end of shelf life of the finished product that is 24 hours with no degradation or trends evident in the data.

No post approval stability protocol or commitment was provided for the active substance. Given that the active substance is not isolated in routine manufacture, this is acceptable.

Comparability exercise for Active Substance

Since Cuprymina is not intended for direct administration without conjugation to carrier molecules, no clinical data with the use of Cuprymina alone has been submitted; therefore no comparability exercise was necessary.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim was to develop a manufacturing process that allows obtaining a sterile finished product with a very low content of metallic impurities, to ensure the intended performance of the product that is its radiolabelling capacity.

Cuprymina is supplied in HCl 0.1N. The performance of the finished product is linked to its capacity to label specific carrier molecules. This capacity can be reduced by the presence of metallic impurities, therefore part of manufacturing process development focused on ensuring that the synthesis unit and dispensing module are cleaned by a valid procedure after every manufacturing run.

Adventitious agents

No starting materials, raw materials or reagents are of human or animal origin. There are no excipients of human or animal origin used in the finished product. Therefore, there is no risk of BSE/TSE transmission via this product.

Manufacture of the product

The manufacturing process includes four steps:

- dilution
- dispensing
- sterilisation
- packaging

The finished product is prepared in a computer-assisted dispensing unit. Activity and volume are measured as soon as the bulk solution of the active substance is delivered from the synthesis module. After measurement of radioactivity and volume, the active substance solution is diluted with 0.1 N HCl to a volume between 10-60 mL according to client request and in order to have a concentration of 925 MBq/mL ± 5% at 01:00 am CET on the date of manufacture. The dispensing unit is located in a radiation shielded enclosure. The product is sterilised by terminal sterilisation according to an accelerated cycle shown to be at least equivalent to the standard sterilisation cycle of the Ph.Eur.

The in process control limits are justified in line with the intended use of the product and with batch data where appropriate.

The manufacturing process has been validated on six industrial scale batches of the product, representative of the minimum and maximum batch size, and the process is considered validated.

Reassurance is also gained from the fact that the process is monitored remotely for every batch of the product, meaning that any deviations may be immediately investigated.

Product specification

The specification of the finished product covers appropriate parameters for the dosage form.

The product is tested:

- pre-release for appearance by visual inspection, radioactive concentration (at calibration time and date) by ionisation chamber, radionuclidic identification by gamma spectroscopy (Ge dectector), radionuclidic purity by gamma spectroscopy (Ge dectector), radiochemical purity and specific radioactivity by TLC, chemical purity by polarography, molarity and pH by potentiometry, bacterial endotoxin by LAL (Ph. Eur.) and control of sterilisation.
- post-release for half-life by gamma spectroscopy (Ge detector), filter integrity by bubble point test and sterility (Ph. Eur.)

Given the short (12.7 h) half life of ^{64}Cu, the product is released before sterility testing has been performed. Sterility testing is performed after the release of the product when the product is no longer radioactive. Given the control on the sterilisation process demonstrated through process validation studies, this is acceptable.

The analytical methods have been satisfactorily described and validated.

Batch analysis data were presented for process validation batches. All results comply with the specification.

Stability of the product

Stability studies were conducted on five batches according to the ICH stability guideline.

In addition to the stability test that indicates the stability at the recommended storage condition of 25°C ± 2 °C, an accelerated stability study a 40 °C has been performed to evaluate the effect of short term excursion outside the label storage conditions and another study at 0 °C has been performed for Cuprymina intended to be shipped by airplane in a condition of 0 °C. Whilst these data are considered useful, they are insufficient to support such excursions in routine use. Therefore the shelf life approved for the product will not include approval for excursions from the labelled storage conditions.

The results of stability studies support the shelf-life and storage conditions as defined in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The validity of the analytical methodologies used for testing of isotopic impurities and metallic impurities of the starting material ^{64}Ni was questioned during the procedure. ^{64}Ni must comply with extremely tight specifications, especially regarding purity that relate to isotopic and chemical purity of the final drug product. The applicant provided additional data to confirm the validity of these methods. This was considered acceptable.

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

There were no non-clinical studies submitted in the application except from a biodistribution study in nude mice to evaluate dosimetry. The applicant submitted a review of the published literature in non-clinical studies with ^{64}Cu radiolabelled carrier molecules as support for the clinical utility of ^{64}Cu.

2.3.2. Pharmacology

A review of the available pharmacodynamic data of ^{64}Cu was submitted in the form of literature references. This review addressed the mechanics of Cu intracellular transport and the biochemistry of ^{64}Cu relating to nuclear medicine imaging and therapy.

Primary pharmacodynamic studies

Nuclear medicine imaging

Use as a tracer and in preclinical oncology studies

^{64}CuCl2 is sufficiently labile to permit rapid synthesis of Cu^{+2} compounds simply by addition of the ligand at an appropriate pH at room temperature[1] . Simple compounds labelled with ^{64}Cu have also been used in preclinical oncology studies. For example, ^{64}CuCl2 has been used as a probe for imaging mouse extra-hepatic hepatoma expressing a mouse copper transporter[2] . ^{64}Cu dithiosemicarbazone (ATSM) was shown to reduce the clonogenic survival rate in vitro of mouse lung carcinoma cells in a dose-dependent manner[3] . ^{64}Cu–labelled monoclonal antibodies have been used to characterise the internalisation properties of radio-immunoconjugates in vitro, to obtain their in vivo distribution profile and to calculate mouse xenograft dosimetry when designing preclinical therapy studies[4] .

Systemic administration of hypoxia-selective ^{64}Cu-ATSM has increased significantly the survival time of hamsters bearing human GW39 colon cancer tumours, survival being 135 days in treated hamsters vs 20 days in untreated animals[5].

Preclinical studies on Hypoxia

Generally shorter-lived isotopes are used to measure blood flow and hypoxia, for example, the ^{62}Cu-PTSM and ^{62}Cu-ATSM have been evaluated to image hypoxic tissue in myocardium[6] and tumours[7] respectively. ^{64}Cu-ATSM in rat tumour shows high uptake in liver and kidney, indicating these as clearance organs for ^{64}Cu-ATSM. The early rapid uptake of ^{64}Cu ATSM in the brain may be due to the high membrane permeability of ^{64}Cu-ATSM[8] . ^{64}Cu-ATSM has exhibited potential as diagnostic modality for the detection of tumour ischemia[9, 10]. In ischemic rat heart tissue, ^{64}Cu-ATSM showed high accumulation whereas perfusion marker ^{11}C-acetate showed low accumulation[11]. ^{64}Cu-PTSM has been used in the detection of cerebral and myocardial blood flow perturbations and in fibrosarcoma therapy[12].

Somatostatin and analogues

Peptide analogues of somatostatin have been labelled with a variety of radionuclides, including isotopes for gamma scintigraphy and PET imaging, as well as β–emitters for peptide receptor radionuclide therapy applications. Tracer ^{64}Cu-DOTA-labelled somatostatin analogues have been synthesized and evaluated in rats[13]. Comparison of four ^{64}Cu-TETA-labelled somatostatin analogues in vitro and in tumour bearing rats has been performed[14], with the goal to optimize the peptide portion of the radiopharmaceutical for target tissue uptake and non-target tissue clearance: among octreotide, Y3-octreotide, TATE and Y3-TATE, ^{64}Cu-TETA-Y3-TATE showed the best targeting and clearance properties. A Y3-TATE-based ^{64}Cu radiopharmaceutical containing a cross-bridged macrocyclic chelator, ^{64}Cu-CB-TE2A-Y3-TATE, displayed improved target tissue uptake and blood and liver clearance compared to ^{64}Cu-TETA-octreotide and ^{64}Cu-TETA-Y3-TATE in vitro and in vivo in tumour bearing rats[15].

Monoclonal antibodies (mAb) and peptides

Radiolabeled peptides and monoclonal antibodies are class of molecules for the targeted imaging and therapy of tumours. ^{64}Cu-DOTA-cetuximab has been used to image EGFR-positive xenograft tumour models[16].

Radiolabeled arginine-glycine-aspartate (RGD) peptides that are integrin specific can be used for non invasive imaging of integrin expression level as well as for integrin-targeted radionuclide cancer diagnosis and therapy. The ^{64}Cu-DOTA-E{E[c(RGDfK)]2}2 has been used for peptide receptor radionuclide imaging and therapy of integrin-positive tumours[17] . The efficacy of the ^{64}Cu-labelled streptavidin to detect early or delayed apoptosis has been studied in small animal PET to evaluate cancer treatment protocols[18].

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were submitted.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted.

2.3.3. Pharmacokinetics

No study reports on pharmacokinetics were submitted. A review of the literature on the pharmacokinetic behaviour of ^{64}Cu was submitted.

Bile is the major pathway for the excretion of copper[19].

Dosimetry

Dosimetry of the labelled radiopharmaceutical will depend on the pharmacokinetics of the carrier to be labelled.

In order to generate data for the evaluation of the internal radiation dosimetry in humans, an evaluation of the internal radiation resulting from the free Copper (^{64}Cu) that could be administered unconjugated or release from the protein conjugates was carried out in mice. 100 male nude mice were administered a single i.v. dose of Copper (^{64}CU) chloride at a nominal dose level of 15 MBq/kg bodyweight corresponding to 4 ng/kg of Cu. Tissues were sampled at 2min, 30min, 60min, 4hr, 6hr, 12hr, 24hr, 2days, 4 days and 6 days. The results are shown in Tables 3 and 4 for the distribution of $^{64}CuCl_2$ in mice and the estimation of the human internal radiation dosimetry, respectively, performed

in accordance with the dosimetry estimates based on a mouse distribution study. The approach used was based on OLINDA - Organ Level INternal Dose Assessment Code (copyright Vanderbilt University, 2003)[20] . Most organs contained radiation at the 2 min sample point.

Table 3: Distribution of [^{64}Cu]CuCl2 in mice tissue after intravenous injection (15MBq/Kg) corresponding to 4 ng/Kg of nat.Cu

number of rats	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Organs	% of dose									
	2min	30min	60min	4hr	6hr	12hr	24hr	2days	4days	6days
whole blood*	60.3	17.6	3.4	2.7	2.3	5.6	4.9	4.7	2.3	1.9
liver*	14.1	38.1	54.1	57.7	52.6	52	29.6	15	5.5	4.8
skeletal muscle	11	14.1	7.7	4.9	4.3	3.4	5	8		
bone	6.3	5.5	3	3	2.3	3.6	3.9	4.1		
skin	5.4	8.6	7	6	3.6	3.5	4.5	6.1		
intestinal tract	4.7	6.5	4.9	7	5	4	7	3.6		
erythrocytes*	2.5	1.1	1	1	0.2	0.9	1.1	0.5	0.5	0.6
kidneys*	1.9	2.5	5	4.8	4.6	2.2	1.5	1.4	0.8	0.7
lungs	1.7	2.2	0.7	0.22	0.2	0.24	0.49	0.49		
hearts	0.76	0.45	0.13	0.09	0.09	0.11	0.14	0.25		
testes	0.57	0.41	0.3	0.34	0.36	0.59	0.58	0.67		
spleen	0.35	0.23	0.1	0.11	0.06	0.09	0.13	0.15		
pancreas	0.1	0.34	0.15	0.14	0.27	0.17	0.18	0.18		
lymphonodes			0.08	0.03	0.03		0.06			
brain	0.102	0.042	0.015	0.016	0.014	0.02	0.032	0.05		
adrenals			0.005	0.006	0.005		0.0013			
thyroid			0.003	0.002	0.001		0.003	0.006		
pituitary			0.002	0.002	0.002		0.003			
urine				0.78	0.52	1.1	1.8	4.8		
faeces and intestinal contents	0.08	1.65	7.4	10.7	14	14.1	27.2	53.1		
%of dose accounted for	109.9	99.3	95	99.5	90.5	90.6	87.9	102		

Table 4: Absorbed dose per unit activity administered

Absorbed dose per unit activity administered (mGy/MBq)							
Organ	Adult male (70Kg)	Adult female (60Kg)	15 years	10 years	5 years	1 years	New Born
Adrenals	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Brain	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Breasts	5.96E-04	7.30E-04	7.32E-04	1.33E-03	2.04E-03	3.84E-03	7.76E-03
Gallbladder Wall	1.92E-03	2.30E-03	2.19E-03	2.78E-03	4.53E-03	9.17E-03	1.58E-02
LLI Wall	1.49E-02	1.60E-02	1.95E-02	3.40E-02	5.69E-02	1.12E-01	2.91E-01
Small Intestine	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Stomach Wall	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
ULI Wall	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Heart Wall	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Kidneys	8.85E-03	9.69E-03	1.07E-02	1.51E-02	2.24E-02	4.01E-02	1.06E-01
Liver	2.11E-02	2.82E-02	2.83E-02	4.36E-02	6.49E-02	1.26E-01	2.94E-01
Lungs	1.78E-03	2.33E-03	2.45E-03	3.51E-03	5.26E-03	9.99E-03	2.40E-02
Muscle	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00

Ovaries	0.00E+00	3.14E-03	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Pancreas	2.67E-03	3.10E-03	3.65E-03	7.16E-03	9.55E-03	1.99E-02	6.37E-02
Red Marrow	5.81E-03	5.65E-03	6.70E-03	1.18E-02	2.42E-02	5.86E-02	1.98E-01
Osteogenic Cells	2.02E-03	2.69E-03	2.63E-03	4.26E-03	7.18E-03	1.72E-02	5.49E-02
Skin	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Spleen	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Testes	4.63E-02	0.00E+00	1.14E-01	9.07E-01	1.05E+00	1.41E+00	2.02E+00
Thymus	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Thyroid	1.29E-04	1.56E-04	1.89E-04	2.92E-04	5.93E-04	1.13E-03	1.78E-03
Urinary Bladder Wall	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Uterus	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00
Effective dose (Sv/1 MBq administered)							
	Adult male	**Adult female**	**15 years**	**10 years**	**5 years**	**1 years**	**New Born**
	9.62E-02	7.12E-02	1.68E-01	8.54E-01	1.05E+00	1.56E+00	2.73E+00

2.3.4. Toxicology

The applicant presented a review of the available literature references of toxicology data of copper (Cu) and ^{64}Cu. The majority of information concerns the oral route of administration and copper sulphate salt.

Single dose toxicity

From the data reported it appears that mice are less susceptible to copper than rats. In the various acute studies, as the lethal dose is approached, signs of copper toxicity include excessive salivation, vomiting, diarrhoea, gastric haemorrhage, hypotension, haemolytic crisis, convulsions and paralysis.

Repeat dose toxicity

In the short-term 15-day feeding studies, there were no deaths in concentrations of Cu in food and/or water up to 16,000 ppm, the highest level of dietary inclusion (equivalent to 324 mg Cu/kg bw/day in male rats, 285 mg Cu/kg bw/day in female rats, and 717 and 781 mg Cu/kg bw/day in male and female mice, respectively). Microscopic findings in rats at 2,000 ppm and above included hyperplasia and hyperkeratosis of the squamous mucosa of the limiting ridge separating the forestomach from the glandular stomach. A similar finding was observed in mice but the severity was minimal. Rats also showed chronic liver inflammation, and effects on haematopoietic cells of the bone marrow and spleen, at 8,000 ppm and above, and kidney findings similar to those seen in the drinking water studies, at 2,000 ppm and above. The lowest NOEL for male and female rat is 1000 ppm equivalent to 23 mg Cu/kg bw/day. The lowest NOEL for male and female mice is 1000 ppm equivalent to 43 or 53 mg Cu/kg bw/day. The short-term feeding study data were used to set dose levels for the 90-day studies[21].

Administration of copper sulphate did not cause any adverse effects on any of the reproductive parameters measured (oestrous cycle length, sperm morphology and sperm motility) of either species.

Table 5: Summary of the relevant NOAELs

Study/species	Route	NOAEL mg/kg b.w.	Reference
90 days/mice	diet	97 537 (for the effect on	Hebert 1993[21]

		fertility)	
90 days/rat	diet	16 67 (for the effect on fertility)	Hebert 1993[21]
40-44 weeks/rat	diet	27 (LOEL)	Harrisson et al. 1954[22]
12 m/dog	diet	15	Shanaman, 1972[23]
1month+29 days/mice	diet	53	Lecyk, 1980[24]
9 month + 3 month/mink	diet	6	Auerlich et al, 1982[25]
10 days/rat	os	30	De La Iglesia, 1982[26]
26 days/rat	i.p.	1	Chattopadhyay et al., 1999[27]
Daily intake	diet	1-2 mg/person/day	
Body burden		50-120 mg	
Serum concentration		0.86 mg/L	Gonzalez et al., 1990[28]
Blood concentration		1.1 mg/L	Iyengar et al., 1988[29]
PTDI		0.5 mg/kg b.w.	WHO, 1982[30]

Neurotoxicity

A few studies report the neurological effects of copper compounds. In rats, oral exposure to copper (II) sulphate in two studies did not affect the results of the behavioural tests, but did alter brain neurochemistry. Injection of copper (II) chloride altered levels of neurotransmitters in the brain of rats.

Genotoxicity

There were no genotoxicity studies reported in which copper salts were administered i.v.. Published reports on in vitro and in vivo genotoxicity studies that investigated long term effects of high dose levels of copper and a two-year dietary administration of copper were submitted. In vitro studies showed that copper was generally not mutagenic in test bacteria TA98, TA100 and TA102 strains of Salmonella typhimurium with and without exogenous metabolic activation[31,32]. However, there was evidence of genotoxicity in some studies where copper(II)sulphate caused an increase of unscheduled DNA synthesis in cultured rat hepatocytes and copper(II) 8-hydroxyquinolone being weakly mutagenic in some strains of Salmonella and E.coli. Dietary dose levels equivalent to 250 mg Cu/kg bw/day for up to 52 weeks duration were associated with initial (week 6) liver damage including hypertrophic, hyperchromatic parenchymal cells, necrosis and marked inflammatory reaction, and kidney damage to the proximal convoluted tubule. Both liver and kidney showed complete recovery between 9 and 15 weeks of continued copper administration. The two-year dietary study showed that there was no increase in incidence of tumours after two years dietary administration of potassium sodium copper chlorophyllin or copper sulphate[33].

Carcinogenicity

The applicant submitted a literature review of carcinogenicity studies. The studies are summarised in Table 6:

Table 6: Summary of carcinogenicity studies related to copper administration

Study type	Species	Route	Duration	Test material Dose levels	Groups/sex/ strain	GLP guidelines	NOEL	Reference
Long term-carcinogenicity	Rat	Diet	104 weeks	Potassium sodium copper chlorophyllin 0.1, 1 or 3% equivalent to 53, 530 and 1600 ppm copper in the diet (=2.7, 27 or 80 mg Cu /kg bw/ day)	20 m ale a nd 20 female S prague-Dawley rats	Prior to GLP	NOEL for Potassium sodium copper chlorophyllin 3% (=80mg Cu/kg bw/day) for tumorigenic effects.	Harrisson, et al., 1954, *J Amer Pharm Ass*, Vol. XL111, **12,** 722-737.
Chronic study	Rat	Diet	42 weeks	Copper sulphate 530,or 1600 ppm (=27 or 80 mg Cu/kg bw/day)	25 m ale a nd 25 female S prague-Dawley rats	Prior to GLP	<27 mg Cu/kg bw/day No tumorigenic effect	Harrisson, et al., 1954,. *J Amer Pharm Ass*, Vol. XL111, **12,** 722-737.
Chronic study,	Rat	Diet	42 weeks	Copper gluconate 1600 ppm (=80 mg Cu/kg bw/day)	25 m ale a nd 25 female S prague-Dawley rats	Prior to GLP	No tumorigenic effect	Harrisson, et al., 1954,. *J Amer Pharm Ass*, Vol. XL111, **12,** 722-737.
Carcinogen co-administration/	Rat	Diet	16 or 19 months.	*p*-dimethylamino-benzene at 0.9% diet with or without 0.5% copper acetate or 2% ferric citrate	Outbred l aboratory rats an d heterozygous laboratory rats	Prior to GLP	Co-administration of copper markedly reduced the incidence of liver tumours caused by *p*-dimethylaminobenzene	Howell, J.S.(1958) Br. J. Cancer **12**: 594-610.
Carcinogen co-administration	Rat	Diet	9 months	800 mg Cu/kg diet copper sulfate (equivalent to 40 mg Cu/kg body weight), dimethylnitrosamine (DMN) in the drinking water (50 mg/kg) or acetylaminofluorene AAF in the diet (0.06%) in both cases for 4 days in every 8 for 6 months, or no further treatment	males		The incidence of AAf induced extrahepatic neoplasms was apparently reduced by the excess copper diet (5/30 vs 11/27 in the low copper group. Toxic effects were seen at 40 mg/kg. Exposure and group size were inadequate to assess the carcinogenic potential of copper sulphate, but the data suggest that it may have an inhibitory effect on DMN induced kidney tumours and AAF induced	Carlton and Price, 1973. *Food Cosmetics Toxicol*, 11, 1973, 827-832

Study type	Species	Route	Duration	Test material Dose levels	Groups/sex/ strain	GLP guidelines	NOEL	Reference
							extrahepatic tumours.	
Special study Copper toxicosis and tolerance in the rat	Rat	Diet	52 weeks	Copper sulphate 3000 ppm Cu (= 250 mg Cu/kg bw/day) for 1 year Copper sulphate 3000 ppm Cu (= 250 mg Cu/kg bw/day) for 15 weeks, followed by 6000 ppm Cu for 3 weeks. Naïve rats given 6000 ppm after 15 weeks on control diet	Male w eanling Wistar rats	Not GLP Non-guideline study.	Not tumourigenic after 1 year administration at 3000 ppm. Increasing the dose from 3000 ppm to 6000 ppm after 15 weeks showed no adverse effects. Treatment of naïve rats showed hepatocellular necrosis.	Haywood and Loughran (1985), *Liver*, 5, 267-275.
Special study Copper acetate-pulmonary tumor response in strain A mice	Mouse	i.p.	8 weeks (3 times a week) sacrifice after 30 weeks from the first treatment	Copper acetate 36, 90 and 180 mg/kg Positive control=urethane 20 mg7animal	Groups of 10 M and 10 F StrainA/Strong mice	Not GLP	NOEL for lung tumours = 180 mg/kg bw/day	Stoner et al. *Cancer Research*, 36, 1744-1747. 1975

Reproduction Toxicity

The applicant submitted a review of the literature on reproduction toxicity. In some studies in rats, chronic oral exposure to 27-120 mg/kg bw per day of copper resulted in altered weight and/or histology of the testes, seminal vesicles, uterus or ovaries. Other studies have demonstrated that exposure to copper compounds during gestation induced embryo/foetotoxic effects at doses of 12 mg of copper/kg body weight and above[34].

Local Tolerance

The applicant did not submit studies on local tolerance.

Other toxicity studies

2.3.5. Ecotoxicity / environmental risk assessment

An ERA specifically addressing the effect of Cuprymina on the environment has not been conducted. This is acceptable as all radiopharmaceuticals should be handled and disposed in accordance with

national regulations. The ERA concentrated on the safe synthesis, transport and handling of the radionuclide.

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation. Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

2.3.6. Discussion on non-clinical aspects

No new animal studies were conducted with Cuprymina except for the biodistribution study in nude mice which provides data on internal radiation resulting from free ^{64}Cu that could be administered unconjugated or released from the conjugates.

Pharmacokinetics of Cuprymina was investigated in mice. Following intravenous administration, at the beginning most organs contained an amount of radioactivity which represented their content of ^{64}Cu-laden blood. Liver, kidney and the intestinal tract reached their maximal content of ^{64}Cu within the first few hours, and then radioactivity steadily diminished. Part of the decrease can be attributed to excretion of ^{64}Cu into the bile, urine and faeces.

Blood radioactivity decreased from 60.3 % to 3.4 % after 1 hour, and then it decreased to 1 % after 6 hours, and increased to 5.6 % and 4.9 % after 12-24 hours.

Copper (^{64}Cu) chloride is distributed mainly in the liver and kidney and the pattern of radioactivity in the blood parallels the pattern of radioactivity in the liver. Almost the entire ^{64}Cu rapidly leaves the blood and enters the liver and kidney.

Maximum liver uptake was at 4 hours after injection at 57.7 % of the administered dose. Subsequently, copper re-emerges in plasma and is distributed to other organs.

Non-clinical data show that unconjugated ^{64}Cu accumulates in kidney and renal radiation damage, liver toxicity and haematotoxicity are likely to be the most important toxicity (and dose limiting factors) to be observed in the clinical situation.

No animal toxicity studies were conducted with Cuprymina. Most of the experimental data on the toxicity of copper comes from studies in rats. Its main risk derives from the emission of high energy β radiation. Liver, gastrointestinal tract and kidney are the target organs for copper toxicity after single and repeated dose administration. Many international bodies assessed copper genotoxicity and carcinogenicity concluding that there is no conclusive evidence that copper may be mutagenic or carcinogenic. The Scientific Committee on Food of the European Commission (2003) recommend a Dietary Allowances of 0.9 mg copper/day in adult males and females and established a Tolerable Upper Uptake level of 5 mg/day, allowing a huge safety margin in comparison to copper amount administered by Cuprymina.

Cuprymina is a precursor to be used for in vitro radiolabelling of carrier molecules and is not directly injected in patients. Because of the very low systemic exposure to ^{64}Cu (maximal dose administered is 2.77 GBq), no primary or secondary pharmacodynamic effect is expected either from the unconjugated radionuclide or from the cold copper chloride.

The applicant did not submit local tolerance studies. This is acceptable as Cuprymina is not to be directly injected in patients.

Cuprymina is not considered to be associated with unacceptable environmental risks provided current regulations related to the handling and disposal of radiopharmaceuticals are adhered to. The SmPC provided advice and guidance on how to use the product (section 4.4 special warning and precautions of use) and how to handle the radioactive waste (section 6.6 special precautions for disposal and other handling).

2.3.7. Conclusion on the non-clinical aspects

The mutagenicity, carcinogenicity and radiotoxicity are not a concern for Cuprymina as the amount of copper utilised in the diagnostic protocol for Cuprymina (4 ng/kg bw corresponding to 240 ng/60 kg person/treatment) is considered negligible. It can be concluded that there is no appreciable additional risk deriving from the use of ^{64}Cu in human.

No supplementary animal studies are needed because safety issues can adequately be evaluated from the literature and considering that single and repeated dose toxicity studies will be provided for the carrier medicinal products using the ^{64}Cu radiolabel.

For the purpose of an application for a radiopharmaceutical for radiolabelling, the non-clinical aspects of Cuprymina have been adequately addressed.

2.4. Clinical aspects

2.4.1. Introduction

Cuprymina is a radiopharmaceutical precursor, and is itself not intended for direct administration but for radiolabelling of a carrier molecule. The applicant submitted a literature review on the clinical utility of Cuprymina. The following Table 7 presents a review of the published literature submitted by the applicant, reporting data on some Cu isotopes-conjugated compounds to support the claim for clinical utility of ^{64}Cu radiopharmaceutical precursor.

2.4.2. Clinical efficacy

The following Table 7 presents a review of the published literature submitted by the applicant, reporting data on some Cu isotopes-conjugated compounds to support the claim for clinical utility of ^{64}Cu radiopharmaceutical precursor.

Table 7: Human studies with Cu-labelled radiopharmaceuticals

Radio-pharmaceutical	Aim	Disease	N° of Patients /Age	AE	Results
Study 1[35]: ^{64}Cu-TETA-OC; ^{111}In-DTPA-OC	Imaging	NET	8 45–70 y	No	^{64}Cu-Teta-OC detects more lesions than conventional imaging methods
Study 2[36]: ^{60}Cu-ATSM	Imaging	Non-small-cell Lung carcinoma	19 55–85 y	No	60Cu-ATSM was able to discriminate subject responders to therapy from non-responders
Study 3[37]	Imaging	Cervical	14	No	Discrimination of patients likely to

Radio-pharmaceutical	Aim	Disease	N° of Patients /Age	AE	Results
^{60}Cu-ATSM		cancer	23–84 y		develop tumour recurrence
Study 4[38]: ^{60}Cu-ATSM ^{18}F-FDG	Imaging	Rectal Cancer	19	No	^{60}Cu-ATSM-PET may be predictive of survival and tumour response to neo-adjuvant chemoradiotherapy
Study 5[39]: ^{61}Cu-ATSM	Treatment Planning	Head and neck squamous cell carcinoma	1 NA	NA	Methodology may have significant value in the clinical implementation of continuous dose painting strategies utilizing dose redistribution
Study 6[40]: ^{60}Cu-ATSM	Imaging	Cervical cancer	15 mean, 54 years	No	Correlation of PET results with hypoxia-related molecular markers
Study 7[41]: ^{62}Cu-ATSM ^{15}O-gas ^{15}O-water	Imaging	Major CVD	10 59 to 79 y	No	^{62}Cu-ATSM provided information on CBF distribution and local elevation of OEF in patients with chronic CVD
Study 8[42]: ^{64}Cu-ATSM ^{60}Cu-ATSM	Imaging	Cervical Cancer	10 33 to 79 y	No	Image quality with 64Cu-ATSM was better than that with 60Cu-ATSM
Study 9[43]: ^{62}Cu-ATSM ^{18}F-FDG	Imaging	Locally advanced head and neck cancer	17 57 to 85 y	No	^{62}Cu-ATSM uptake may be a predictive indicator of tumour response to chemoradiotherapy
Study 10[44],[45]: ^{62}Cu-PTSM ^{15}O-water	Imaging	Neurological disease	10 18 to 75 y	No	^{62}CuPTSM can be used widely for evaluation of brain perfusion with PET (1994) and Graphical Analysis (Patlak plot) suggested that can be analyzed by the three-compartment model with negligible k4 (1996)
Study 11[46]: ^{64}Cu MAb-1A3	Imaging	Colorectal carcinoma	36	No	Detection of 71% of confirmed tumour sites
Study 12[47]: ^{62}Cu-ATSM ^{62}Cu-PTSM ^{18}F-FDG	Imaging	Patients with lung nodules (> 1 cm) suspicious for malignancy	2	No	Feasibility of performing ^{62}Cu-ATSM and ^{62}Cu-PTSM PET together with FDG PET/CT during a single imaging session.
Study 13[48]: ^{62}Cu-ATSM ^{18}F-FDG	Imaging	4 Normal; 6 Lung Cancer	10	No	The negative correlation between blood flow and flow normalized 62Cu-ATSM uptake

Radio-pharmaceutical	Aim	Disease	N° of Patients /Age	AE	Results
					suggests an enhancement of retention of 62Cu-ATSM by low flow.
Study 14[49]: ^{67}Cu-2IT- BAT-Lym1	Therapy	NH lymphoma	12	No	Response rate to therapy = 58%
Total number of cases			182		

2.4.3. Pharmacokinetics

No clinical pharmacology studies were submitted with this application.

2.4.4. Pharmacodynamics

No clinical pharmacology studies were submitted with this application.

2.4.5. Discussion on clinical pharmacology

The lack of clinical pharmacology studies is considered acceptable. The pharmacokinetics of a radiopharmaceutical would be dependent on the carrier molecule labelled with Cuprymina. The pharmacodynamics of a radiopharmaceutical would also be dependent on the carrier molecule and on the method of conjugation used to link it to the radioisotope.

The applicant has provided a discussion to justify the low likelihood of the presence of free Cuprymina in the body, following administration of a Cuprymina labelled radiopharmaceutical. This is based on the high labelling index observed with molecules that have been labelled with Cuprymina up to now. The applicant has also discussed the biological pathway of copper in the body to justify that the normal homeostatic mechanisms would prevent an overdosage of copper, which is not expected considering the negligible dose of copper that would be administered with the use of Cuprymina.

2.4.6. Conclusions on clinical pharmacology

The clinical pharmacology of Cuprymina will be dependent on the carrier molecule used and relevant clinical pharmacology data with Cuprymina will have to be submitted separately with the different carrier molecules. For the purpose of an application for a radiopharmaceutical for radiolabelling, the clinical pharmacology of Cuprymina has been adequately addressed.

2.4.7. Clinical Utility

The applicant has discussed and submitted clinical data to support the clinical utility of Cuprymina or ^{64}Cu radionuclide in imaging of tissue hypoxia and detection of primary tumour sites and metastases.

Imaging of tissue hypoxia

The applicant presented several studies which used dithiosemicarbazone (ATSM) labelled with copper radioisotopes as a hypoxia marker for PET scanning, as well as the factors contributing to the trapping

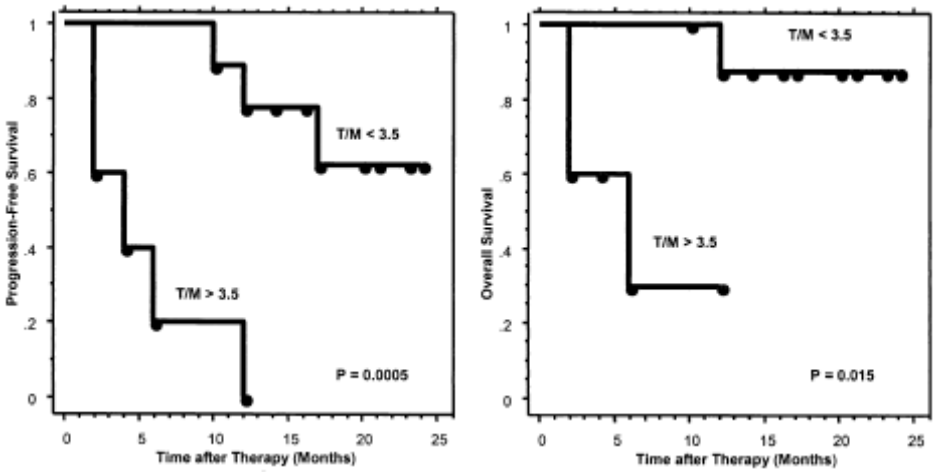
of Cu(II)-ATSM in hypoxic cells. The following studies summarise the data in support of the claim of clinical utility in imaging of tissue hypoxia for Cuprymina:

Study 13: ***Takahashi N., Fujibayashi Y., Yonekura Y., et al. (Annals of Nuclear Medicine Vol 14, No 5, 323-328, 2000)*** The first human report of copper labelled–ATSM, evaluated in 4 normal subjects and 6 patients with lung cancer. ^{62}Cu was the isotope used in this study. PET was performed with a high-resolution, whole body PET scanner. To compare 62Cu-ATSM images with blood flow and glucose metabolism of tumours, ^{15}O-water and FDG-PET was performed within 1 week. ^{62}Cu-ATSM rapidly cleared from the blood, reaching a stable activity after the injection. Little uptake was observed in the lung; the myocardial uptake was small; but the liver uptake was considerable. There was no correlation between ^{62}Cu-ATSM and the blood flow pattern except in one patient. No correlation was found between ^{62}Cu-ATSM and FDG. In 3 of 4 patients, a negative correlation was found between blood flow and the flow-normalised ^{62}Cu-ATSM uptake ratio.

Study 2: ***Dehdashti F., Mintun M.A., Lewis J.S., et al. (European Journal of Nuclear Medicine and Molecular Imaging, Vol 30, No.6, June 2003)***, assessed the feasibility of clinical imaging with ^{60}Cu-ATSM in patients with non-small cell lung cancer, and also assessed whether pre-treatment tumour uptake of ^{60}Cu-ATSM predicted tumour responsiveness to therapy. Nineteen patients with biopsy-proven non-small-cell lung cancer (NSCLC) were studied by positron emission tomography (PET) with ^{60}Cu-ATSM and fluorine ^{18}F-FDG before the beginning of therapy. ^{60}Cu-ATSM uptake was evaluated semi-quantitatively by determining the tumour-to-muscle activity ratio (T/M). The PET results were correlated with follow-up evaluation (2-46 months). The tumour of one patient had no discernible ^{60}Cu–ATSM uptake, whereas the tumour uptake in the remaining patients was variable. ^{60}Cu–ATSM showed high contrast levels between hypoxic and normoxic tissues and yielded clinically relevant information about tumour oxygenation that was predictive of response to therapy and tumour treatment outcome. A semi-quantitative analysis of the ^{60}Cu–ATSM tumour-to-muscle ratio was able to discriminate subject responders to therapy from non-responders. The mean T/M ratio was significantly lower in responders (1.5±0.4) than in non-responders (3.4±0.8) (P=0.002). An arbitrarily selected T/M threshold of 3.0 discriminated those likely to respond to therapy. Tumour SUV for FDG was not significantly different in responders and non-responders (P=0.7) and did not correlate with ^{60}Cu-ATSM uptake(r=0.04; P=0.9).

Study 3: ***Dehdashti F., Grigsby P.W., Mintun M.A., Lewis J.S., Siegel B.A., Welch M.J. (Int Journal of Radiation Oncology Biol. Phys., Vol 55, No.5, pp 1233-1238, 2003)***, investigated whether tumour hypoxia assessed by PET with ^{60}Cu-ATSM could predict the responsiveness to therapy in 14 patients with cervical cancer. ^{60}Cu-ATSM uptake was evaluated semi-quantitatively by determining the tumour to muscle activity ratio (T/M). All patients also underwent clinical PET with ^{18}F-FDG before institution of therapy. Tumour uptake of ^{60}Cu-ATSM was inversely related to progression-free survival and overall survival (log–rank p=0.0005 and p=0.015, respectively). ^{18}F-FDG uptake did not correlate with ^{60}Cu–ATSM uptake (r = 0.04; P = 0.80) and had no significant difference between patients with hypoxic tumours and those with normoxic tumours. An arbitrarily selected tumour to muscle (T/M) activity ratio threshold of 3.5 discriminated those likely to develop recurrence. The frequency of locoregional nodal metastasis was greater in hypoxic tumours (p=0.03). PET results were correlated with follow-up evaluation (14-24 months). Results are illustrated in Figure 1. Patient survival has an inverse relationship with tumour uptake of ^{60}Cu-ATSM assessed by tumour-to-muscle activity ratio ($p < 0.0005$ and $p < 0.015$ respectively).

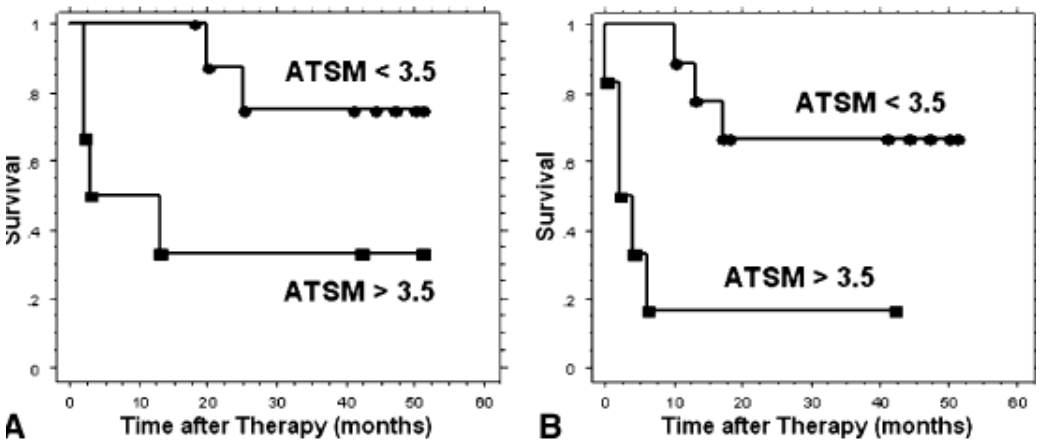
Figure 1: Progression-free survival and overall survival based on ^{60}Cu-ATSM uptake using Kaplan-Meier method



Study 6: ***Grigsby et al, (Mol Imaging Biol 2007, 9:278-283)*.** Fifteen patients with cervical cancer were enrolled in a prospective study aimed to determine if hypoxia-related molecular markers were associated with ^{60}Cu–ATSM retention. These patients underwent evaluation of tumour hypoxia with PET using 60Cu–ATSM. PET imaging data of the patients were compared with the expression of tissue molecular markers, which included vascular endothelial growth factor (VEGF), cyclo-oxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), carbonic anyhdrase IX (CA-9), and apoptotic index. Six patients had hypoxic tumour determined by ^{60}Cu–ATSM and nine had non-hypoxic tumour. The 4-year overall survival estimates were 75% for patients with non-hypoxic tumour and 33% for those with hypoxic tumours (p = 0.04) (Figure 2).

Overexpression of VEGF (p = 0.13), EGFR (p = 0.05), CA-9 (p = 0.02), COX-2 (p = 0.08), and the presence of apoptosis (p = 0.005) occurred in patients with hypoxic tumours. Cox proportional hazards modelling demonstrated hypoxia as determined by ^{60}Cu-ATSM to be a significant independent predictor of tumour recurrence (p = 0.0287).

Figure 2: Overall survival based on ^{60}Cu-ATSM uptake



A. Overall survival for hypoxic (ATSM 9 3.5) vs. non-hypoxic (ATSM G 3.5); p = 0.04.
B. Progression-free survival for hypoxic (ATSM 9 3.5) vs. non-hypoxic (ATSM G 3.5); p = 0.006.

Study 4: ***Dietz D.W., Dehdashti F., Grigsby PW., et al. (The American Society of Colon and Rectal Surgeons; Vol 51: 1641-1648; 2008).*** 19 patients with locally invasive (T2–4) primary or node-positive rectal cancer located <12 cm from the anal verge were evaluated in this pilot study, regarding the utility of ^{62}Cu-ATSM in predicting the prognosis and response of rectal cancers to neoadjuvant chemoradiotherapy. The primary tumour was imaged by positron emission tomography with ^{60}Cu-ATSM, and accumulation of the tracer was measured semi-quantitatively by determining the tumour-to-muscle activity ratio. Eleven patients also underwent clinical positron emission tomography with ^{18}F-fluorodeoxyglucose. Neoadjuvant chemoradiotherapy was then administered within 2 weeks of ^{60}Cu-ATSM-positron emission tomography. Proctectomy was performed six to eight weeks after neoadjuvant chemoradiotherapy and the tumour submitted to pathology for size measurement and staging. Tumour-to-muscle activity ratios were compared with tumour ^{18}F-fluorodeoxyglucose uptake, tumour response to neoadjuvant chemoradiotherapy, and with patient survival. 2 patients were excluded from final analysis. Of the 17 remaining patients, 14 had a reduction in tumour size and 13 were down-staged. The median tumour-to-muscle activity ratio of 2.6 discriminated those with worse prognosis from those with better prognosis. Both overall and progression-free survivals were worse with hypoxic tumours (tumour-to-muscle activity ratio >2.6) than with non-hypoxic tumours (tumour-to-muscle activity ratio ≤2.6; both P<0.05). In addition, 2 of the 3 tumours with no change in size had tumour-to-muscle activity ratios >2.6 (positive predictive value 66 percent), whereas 6 of 14 with decreased size had tumour-to-muscle activity ratios >2.6 (negative predictive value 57 percent). Three of the 4 tumours not down-staged had tumour-to-muscle activity ratios >2.6 (positive predictive value 75 percent), whereas 5 of 13 down-staged tumours had tumour-to-muscle activity ratios >2.6 (negative predictive value 62 percent). The mean tumour-to-muscle activity ratio for down-staged tumours (2.2) was significantly lower than that of non-down-staged tumours (3.3) (P=0.03). The difference in mean tumour-to-muscle activity ratio between downsized (2.3) and non-downsized (2.9) tumours did not reach statistical significance (P=0.36). Tumour ^{18}F-fluorodeoxyglucose uptake (n=11) did not correlate with ^{60}Cu-ATSMuptake (r=0.4; P=0.9) and there was no significant difference in mean tumour ^{18}F-fluorodeoxyglucose uptake between patients with hypoxic tumours and those with normoxic tumours (P=0.3). The results of this small pilot study suggest that ^{60}Cu-ATSM-PET may be predictive of survival and, possibly, tumour response to neoadjuvant chemoradiotherapy in patients with rectal cancer.

Study 9: ***Minagawa Y., Shizukuishi K., Koike I., et al (Ann Nucl Med****; published online 16 Feb 2011).* This pilot study was conducted to determine whether there was a relationship between the uptake of ^{62}Cu-ATSM and response to chemoradiotherapy in patients with locally advanced head and neck cancer. In patients with (non CR) and without (CR) residual/recurrent tumours at 2-year post irradiation, the statistical significance of the differences in tumour ^{62}Cu-ATSM SUVmax, T/M ratio, ^{18}F-FDG SUVmax and tumour volume were analyzed using Student's t test and Welch test. The relationship between clinical outcome and ^{62}Cu-ATSM/^{18}F-FDG uptake patterns was analyzed using Kruskal–Wallis test. The correlation between SUVmax of ^{62}Cu-ATSM and ^{18}F-FDG was compared by Spearman's rank correlation test. Two of the 17 patients that were enrolled in our study were excluded from the final analysis. Of the 15 remaining patients, 9 patients were free of disease and 6 patients had residual/recurrent tumours. The SUVmax differed significantly (p\0.05) between patients with or without residual/recurrent tumour on 62Cu-ATSM PET/CT. Six of the 10 patients with tumours SUVmax [5.00 had residual/recurrent tumour, whereas all of the 5 patients with tumours SUVmax\5.00 were free of disease. There was no significant difference in FDG uptake between patients with and without residual/recurrent tumour. The results of this pilot study suggested that 62Cu-ATSM uptake may be a predictive indicator of tumour response to chemoradiotherapy in patients with locally advanced head and neck cancer.

Study 8: ***Lewis J.S., Laforest R., Dehdashti F., Grigsby P.W., Welch M.J., Siegel B.A. (J Nucl Med 2008; 49:1177-1182).*** The purpose of this study was to obtain the preclinical data for copper-ATSM, followed by a crossover comparison of PET image quality and tumour uptake with ^{60}Cu-ATSM and ^{64}Cu-ATSM in women with cancer of the uterine cervix. The preclinical toxicology and pharmacology of a copper-ATSM formulation was examined using standard in vitro and in vivo assays, as well as 14-d toxicity studies in both rats and rabbits. For the clinical test–retest imaging study, 10 patients with cervical carcinoma underwent PET on separate days with ^{60}Cu-ATSM and ^{64}Cu-ATSM. Image quality was assessed qualitatively, and the tumour-to-muscle activity ratio was measured for each tracer. The toxicology and pharmacology data demonstrated that the formulation has an appropriate margin of safety for clinical use. In the patient study, the authors report that the image quality with ^{64}Cu-ATSM was better than that with ^{60}Cu-ATSM because of lower noise. In addition, the pattern and magnitude of tumour uptake of ^{60}Cu-ATSM and ^{64}Cu-ATSM on studies separated by 1–9 d were similar. The authors concluded that ^{64}Cu-ATSM appeared to be a safe radiopharmaceutical that can be used to obtain high-quality images of tumour hypoxia in human cancers.

Study 12 (*Wong et al., 2008*) deals with the comparison between ^{62}Cu-ATSM and ^{62}Cu-PTSM. The use of ^{62}Cu presents the advantage of short half-life (=9.7 minutes) allowing multiple acquisitions with different carriers. This is an advantage in terms of radio dosimetry. The study was performed in two patients with lung neoplasm. Patients underwent PET with ^{62}Cu -ATSM and ^{62}Cu-PTSM and F18FDG. Results suggest that the distribution of ^{62}Cu-ATSM, a marker of hypoxia, and ^{62}Cu-PTSM, a perfusion marker, does not change 10 min after injection and that imaging between 10 and 20 min after injection reflect the steady-state.

[50]Chao K.S.C., et al (Int. Journal of Radiation Oncology Biol. Phys., Vol 49, No.4, pp 1171-1182, 2001) demonstrated that it was feasible to include information about hypoxia in Intensity Modulated radiotherapy (IMRT) planning. In this study, the Authors have examined the feasibility of Cu-ATSM-guided IMRT, which may potentially deliver higher dose of radiation to the hypoxic tumour sub-volume to overcome inherent hypoxia-induced radio-resistance without compromising normal tissue sparing.

The papers by ***Deveau et al [51]*** and ***Lucignani et al[52]***, also discuss the potential utility of hypoxic tissue imaging by PET in planning delivery of radiotherapy.

Study 7: ***Isozaki M., Kiyono Y., Arai Y., et al. (Eur J Nucl Mol Imaging, 2nd Feb 2011).*** In this study 10 patients with major cerebral arterial occlusive disease underwent PET with ^{62}Cu-ATSM and 15 O tracers. 7 healthy volunteers also underwent ^{62}Cu-ATSM PET as normal controls. Cerebral blood flow (CBF), blood volume, metabolic rate of oxygen (CMRO2) and oxygen extraction fraction (OEF) were measured by 15O-gas and water studies and compared with early- and delayed-phase ^{62}Cu-ATSM images and delayed to early (D/E) ratio. Dynamic PET acquisition with ^{62}Cu-ATSM provided information on CBF distribution and local elevation of OEF in patients with chronic CVD. The findings of the present study showed the feasibility of the non invasive molecular imaging method for diagnosing misery perfusion with a single venous tracer injection.

Detection of primary tumours sites and metastases

The clinical utility of Cuprymina was discussed with the use of copper-64 labelled TETA-octreotide (^{64}Cu-TETA-Octreotide) for imaging in neuroendocrine tumours; and with the use of copper-64 labelled monoclonal antibody 1A3 in the imaging of colorectal cancer.

Study 1: ***Anderson C.J., et al (J of Nuclear Medicine, 2001; 42:213-221)***-Eight patients with a history of neuroendocrine tumours were imaged by conventional scintigraphy with ^{111}In-DTPA-

Octreotide and by PET imaging with ^{64}Cu-TETA-Octreotide. Blood and urine samples were collected for pharmacokinetic analysis. PET images were collected at times ranging from 0 to 36 h after injection, and the absorbed doses to normal organs were determined.

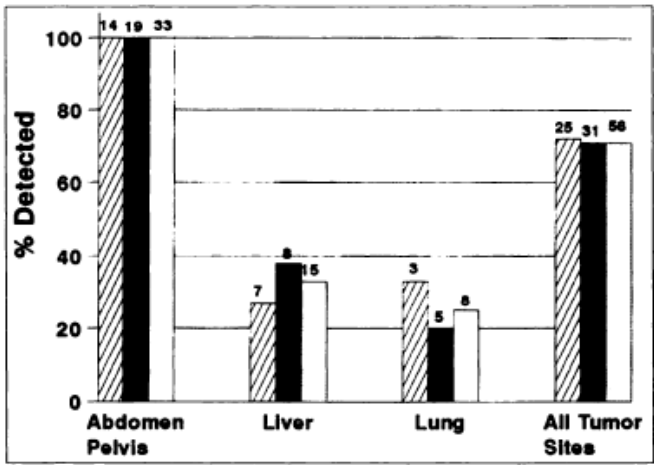
In six of the eight patients, cancerous lesions were visible by both ^{111}In-DTPA-Octreotide SPECT and ^{64}Cu-TETA- Octreotide PET. In one patient, ^{111}In-DTPA-OC showed mild uptake in a lung lesion that was not detected by ^{64}Cu-TETA-OC PET. In one patient, either agent detected no tumours; significantly, pathologic follow-up indicated that the patient had indeed no tumours. In two patients whose tumours were visualized with ^{111}In-DTPA-Octreotide and ^{64}Cu-TETA-Octreotide, ^{64}Cu-TETA-Octreotide and PET showed more lesions than ^{111}In-DTPA-Octreotide. The study confirmed the feasibility of PET imaging of neuroendocrine tumours with the use of ^{64}Cu-TETA-octreotide. In patients with multiple metastases, the ^{64}Cu-TETA-octreotide PET scanning revealed some of the smaller lesions, especially hepatic metastases. Further the ^{64}Cu-TETA-OC PET was able to detect osseous metastases not detected with planar scintigraphy.

Pharmacokinetic studies showed that ^{64}Cu-TETA-Octreotide was rapidly cleared from the blood and that 59.2% +/- 17.6% of the injected dose were excreted in the urine. Absorbed dose measurements indicated that the bladder wall was the dose-limiting organ. Overall, the normal-organ dosimetry suggests that PET imaging with 111 MBq (3 mCi) ^{64}Cu-TETA-OC gave reasonable absorbed doses to normal organs.

Study 11: ***Philpott G.W., et al (J of Nuclear Medicine, 2001; 42:213-221)***, investigated 36 patients with suspected advanced or primary colorectal cancer, by injecting anti-colorectal carcinoma monoclonal antibody (MAb 1A3) labelled with copper-64. All patients had CT scans and ^{18}F-FDG-PET was performed in 18 patients for routine clinical assessment of tumour status. Tumour was confirmed in 21 patients by biopsy and in 8 patients by unequivocal findings on CT, MRI and/or PET with 2-[18F]-fluoro-2-deoxy-D-glucose (FDG, 10mCi).

Of the 56 confirmed tumour sites, PET detected 40 with ^{64}Cu-MAb 1A3 as foci of increased activity (sensitivity = 71%). The abdominal and pelvic disease detection showed equal sensitivity for both MAb-PET and FDG-PET. When the results of the two studies were the same, the presence or absence of tumour was confirmed, but the combination of a negative MAb-PET and positive FDG-PET suggested an inflammatory lesion or other primary tumour. The positive predictive value of the PET 64Cu-MAb-1A3 ranged from 89% to 96 %. Furthermore, PET scan detected 11 new occult tumour sites, including 9 small abdomino-pelvic foci less that 2.0 cm in diameter that were not detected by CT or MRI. The study suggested that PET with ^{64}Cu-MAb may have important applications in clinical oncology, particularly for detecting smaller colorectal tumour foci in the abdomen or pelvis.

Figure 3: Sensitivity for detection of all confirmed tumour sites by MAb-PET.



Results are presented for tumours > 3 cm in diameter (diagonally lined bars); for tumours < 3 cm in diameter (solid bars); and for tumours of all sizes (white bars).

There were no complications, but significantly elevated HAMA titres were found in 28% of the 29 patients tested 1 to 12 months after injection. There was no apparent dose-related effect from 5 to 20 mg MAb 1A3.

2.4.8. Discussion on clinical efficacy

The applicant did not submit a clinical study report to support the claimed indication, which is in line with the requirements of the Directive 2001/83/EC, Annex I, Part III-2.2 and accepted by the CHMP. The applicant provided clinical information from published clinical studies reports using the precursor attached to relevant carrier molecules in support for the claim of clinical utility of the radio-pharmaceutical precursor.

A potential clinical utility of copper 64 was highlighted in two studies discussed above. These include the use of ^{64}Cu-TETA-octreotide in PET scanning of neuroendocrine tumours, which could allow better detection of small lesions and better detection of osseous disease, and the use of ^{64}Cu-MAb 1A3 in PET scanning in colorectal cancer that could allow better detection of small lesions not detected by CT or MRI and enable differentiation of inflammatory lesions from malignant lesions. The differentiation between inflammatory and malignant lesions is sometimes difficult with the commonly used fluorine-18 PET scanning. Therefore these studies do indicate a potential clinical utility for Cuprymina in the molecular imaging of tumours when attached to appropriate carrier molecules.

PET imaging with the use of copper radionuclide-labelled dithiosemicarbazone (ATSM) is of potential clinical utility in the detection of hypoxic areas in tumours, which could predict outcomes to treatment and help plan better delivery of treatment such as radiotherapy. The majority of the studies discussed in support of this application are in relation to hypoxia imaging with copper labelled ATSM. Most of these studies have been done with the radioisotopes copper-60 or copper-62. It is reasonable to foresee that the same carrier molecules may be labelled with Cuprymina (copper-64). All radioisotopes of a chemical element have, by definition, the same chemical properties. Therefore there is theoretical support for the utility of copper-64 in the imaging of hypoxic tissue/ tumours. Further, as discussed above, in at least one study, superiority in image quality has been reported with the use of ^{64}Cu-ATSM compared to ^{60}Cu-ATSM (ref: study 8).

2.4.9. Conclusions on the clinical efficacy

It is the view of the CHMP that clinical utility of Cuprymina attached to the relevant molecular carrier has been demonstrated for tumour imaging and hypoxia imaging. According to Directive 2001/83/EC, as amended, Annex I Part III, this is considered sufficient for the purposes of this application. Further efficacy and safety data in particular indications will be assessed during the marketing authorisation application for carrier molecules proposing to use Cuprymina as a radiolabel.

2.5. Clinical safety

The applicant did not submit clinical safety study reports. Cuprymina is not intended to be administered directly to patients.

The safety of this product as a radiolabelling agent will be evaluated as part of the application of the carrier/linker molecule which proposes to use Cuprymina as a radiolabelling nuclide.

The table below presents the dose at different biological half-lives, both for the maximum activity of the ^{64}Cu and for the standard activity of ^{18}F in ^{18}F-FDG injection (260 MBq).

Table 8: Comparison of ^{64}Cu and ^{18}F radioactivity dose at different half lives

Biological Half-Life (h)	1	10	20	30	50	100	∞
Dose ^{64}Cu (mSv) (2770 MBq)	0.03	0.20	0.28	0.32	0.36	0.41	0.46
Dose ^{18}F (mSv) (260 MBq)	0.01	0.03	0.03	0.03	0.03	0.03	0.03

Based on these estimates, the exposure from ^{64}Cu in a worst case scenario would be 3-15 times greater than a standard injection of ^{18}F.

Dosimetry

The radiation dose received by the various organs following intravenous administration of a ^{64}Cu-labelled medicinal product is dependent on the specific molecule being radiolabelled.

Information on radiation dosimetry of each different medicinal product following administration of the radiolabelled preparation will be available in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

The dosimetry table below is presented in order to evaluate the contribution of non-conjugated ^{64}Cu to the radiation dose following the administration of ^{64}Cu-labelled medicinal product or resulting from an accidental intravenous injection of Cuprymina.

The dosimetry estimates were based on a mouse distribution study and the calculations were effected using OLINDA - Organ Level INternal Dose Assessment Code (See Table 9). Time points for measurements were 2 minutes, 30 minutes, 1 hour, 4 hours, 6 hours, 12 hours, 24 hours, 2 days, 4 days, 6 days.

Table 9: Absorbed dose per unit activity administered

absorbed dose per unit activity administered (mGy/MBq)							
organ	**adult male (70 kg)**	**adult female (60 kg)**	**15 years**	**10 years**	**5 years**	**1 years**	**newborn**
adrenals	0.00	0.00	0.00	0.00	0.00	0.00	0.00
brain	0.00	0.00	0.00	0.00	0.00	0.00	0.00
breasts	0.000596	0.000730	0.000732	0.00133	0.00204	0.00384	0.00776
gallbladder wall	0.00192	0.00230	0.00219	0.00278	0.00453	0.00917	0.0158
LLI wall	0.0149	0.0160	0.0195	0.0340	0.0569	0.112	0.291
small Intestine	0.00	0.00	0.00	0.00	0.00	0.00	0.00
stomach Wall	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ULI wall	0.00	0.00	0.00	0.00	0.00	0.00	0.00
heart wall	0.00	0.00	0.00	0.00	0.00	0.00	0.00
kidneys	0.00885	0.00969	0.0107	0.0151	0.0224	0.0401	0.106
liver	0.0211	0.0282	0.0283	0.0436	0.0649	0.126	0.294
lungs	0.00178	0.00233	0.00245	0.00351	0.00526	0.00999	0.0240
muscle	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ovaries	0.00	0.00314	0.00	0.00	0.00	0.00	0.00
pancreas	0.00267	0.00310	0.00365	0.00716	0.00955	0.0199	0.0637
red marrow	0.00581	0.00565	0.00670	0.0118	0.0242	0.0586	0.198
osteogenic cells	0.00202	0.00269	0.00263	0.00426	0.00718	0.0172	0.0549
skin	0.00	0.00	0.00	0.00	0.00	0.00	0.00
spleen	0.00	0.00	0.00	0.00	0.00	0.00	0.00
testes	0.0463	0.00	0.114	0.907	1.05	1.41	2.02
thymus	0.00	0.00	0.00	0.00	0.00	0.00	0.00
thyroid	0.000129	0.000156	0.000189	0.000292	0.000593	0.00113	0.00178
urinary bladder wall	0.00	0.00	0.00	0.00	0.00	0.00	0.00
uterus	0.00	0.00	0.00	0.00	0.00	0.00	0.00
effective dose (Sv/1 GBq administered)							
	adult male	**adult female**	**15 years**	**10 years**	**5 years**	**1 years**	**newborn**
	0.0962	0.0712	0.168	0.854	1.05	1.56	2.73

Based on a biodistribution study in mice, the impact on male fertility was assessed and showed that the testes received a dose of 0.0463 mGy/MBq. Therefore on the basis that 1 GBq of activity is administered, a dose of 46.3 mGy would be received by the testes. The literature reference[53] states 350cGy as the threshold for temporary azoospermia and 2Gy for permanent azoospermia. In the worst case in which the maximum vial activity is administered (2.77 GBq), 12.7cGy to the testes were estimated.

From the biodistribution table above, it is estimated that ovaries received a dose of 0.00314 mGy/MBq. In the worst case in which the maximum vial activity is administered (2.77 GBq), 0.869 cGy to the ovaries are estimated, more than 7 times less the dose believed to be safe for female fertility as per Ogilvy-Stuart and Shalet (1993)[54].

Disappearance of radioactivity

Considering that each MBq of ^{64}Cu causes a dose rate of 9 nSv/h (at a distance of 2 meters) and that the maximum injected activity is of 2770 MBq, the initial dose rate is 24930 nSv/h.

Assuming that the environmental background value is 150 nSv/h, and requiring that the dose rate due to ^{64}Cu is lower than the environmental background, the condition of negligible radioactivity in the patient is reached, in practice, 4 days after injection (dose rate 132 nSV/h) as shown in Table 10.

Table 10: Condition of negligible radioactivity in the patients

Days after injection (2770 MBq)	0	1	2	3	4	5
Dose rate (nSv/h)	24930	6727	1815	490	132	37

Safety in hospital personnel exposed to Cuprymina

The dose to a person in close contact with the patient is largely due to gamma rays which have a high penetration.

Gamma emission can be compared through the Gamma Constant that states the dose equivalent rate, in mSv h-1 at one meter from a point isotropic source of 1 MBq (Table 11). A comprehensive listing of gamma-dose constants has been published in 1982 by Oak Ridge National Laboratory[55].

Table 11: Gamma-ray dose constants and 95% thickness lead shield, for the relevant Cu isotopes and for ^{18}F.

	^{60}Cu	^{61}Cu	^{62}Cu	^{64}Cu	^{67}Cu	^{18}F
Gamma Constant ($mSv\ h^{-1}\ MBq^{-1}$)	N.A.	1.517E-4	1.881E-4	3.514E-5	2.363E-5	1.851E-4
95% attenuation thickness, Pb (cm)	N.A.	2.001	1.784	1.856	0.230	1.768

The gamma-ray constants are summarised, together with the thickness for 95% attenuation with a lead shield, for the relevant Cu isotopes and for ^{18}F. In consideration of these data, ^{64}Cu does not require significantly more shielding than other isotopes and it has the lowest Gamma Constant of all Cu isotopes that can be used for PET imaging and even lower than ^{18}F, due to the low branching of the β+ emission (511 keV gamma rays) and the only de-excitation gamma ray emitted (1.346 MeV, 0.47% yield). Therefore, for very short exposures (so that decay can be neglected) and comparable activities, doses to the public from ^{64}Cu-radiopharmaceuticals are lower than from ^{18}F-radiopharmaceuticals.

A worst case scenario estimate of the dose to a person in close contact with the patients has been provided, considering the ^{64}Cu gamma dose constant of $1.6x10^{-5}$mSv.MBq^{-1}.h^{-1} at a distance of 1 metre. Assuming that the maximum activity (2770 MBq) is injected to the patient; and that ^{64}Cu is labelled in a molecule with infinite biological half-live (i.e., no elimination by the patient); and a person in contact with the patient is continuously exposed (24h/24h) at a distance of 2 meter; it is estimated that the dose for a person in close contact with the patient is 0.46 mSv.

2.5.1. Discussion on clinical safety

Safety of copper

No clinical safety studies were submitted. This was considered acceptable as Cuprymina is a radioprecursor not intended to be injected to humans.

The doses of Cuprymina expected to be administered are unlikely to be associated with toxicity from a copper overload.

The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. Exposure to ionising radiation is linked with cancer induction and a potential for

development of hereditary defects. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself. The radiation dose received by the various organs following intravenous administration of a ^{64}Cu-labelled molecule is dependent on the specific pharmaceutical being radiolabelled. Information on radiation dosimetry of each different medicinal product following administration of the radiolabelled preparation will be available in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled. This information is included in the Cuprymina SmPC.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely clinical benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended result. Cuprymina is contraindicated in the following cases:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Established or suspected pregnancy or when pregnancy has not been excluded (see section 4.6).

For information on contraindications to particular ^{64}Cu-labelled medicinal products prepared by radiolabelling with Cuprymina, please refer to the Summary of Product Characteristics/package leaflet of each particular medicinal product to be radiolabelled.

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

For information concerning special warnings and special precautions for use of ^{64}Cu–labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled. It must be considered that the radiolabelled medicinal product emits high intensity Auger electrons.

Regarding the dose for a person in close contact with the patient, this is entirely due to the gamma rays (Cuprymina emits 2 gamma rays at 511.0 Kev and 1,345.77 Kev), because β+ and β- emissions have no role due to their very short range.

The ^{64}Cu gamma dose constant is 3.6 x 10^{-5} mSv x MBq^{-1} x h at a distance of 1 meter. Assuming the worst case that the whole maximum activity (2,770 MBq) is injected to the patient and ^{64}Cu is labelled to a molecule with infinite biological half-life (no disposal by the patient) the person is continuously exposed at a distance of 2 meters. With these assumptions the estimated dose for a person in close contact with the patient is 0.46 mSv, which is less than one half of the limit of not exposed people (1mSv/year).

Special precautions for relatives, carers and hospital staff are provided in section 6.6 of the SmPC.

Effects on ability to drive and to use machines following treatment by ^{64}Cu-labelled medicinal products will be specified in the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

Information has been provided in the SmPC regarding the use of chelating agents in the event on an inadvertent overdosage of Cuprymina (section 4.9 of the SmPC).

Appropriate instructions for preparation of Cuprymina are provided in section 12 of the SmPC.

No interactions studies of Copper (^{64}Cu) chloride with other medicinal products have been submitted.

The possible use of chelating therapies could interfere with the use of ^{64}Cu-labelled medicinal products. For information concerning interactions associated with the use of ^{64}Cu-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the radiolabelled medicinal product.

Women of childbearing potential

When an administration of radioactive medicinal products to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Before the use of ^{64}Cu-labelled medicinal products, pregnancy should be excluded using an adequate/validated test.

Pregnancy

The use of ^{64}Cu-labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3 of the SmPC).

Breastfeeding

Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to the choice of the most appropriate radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, a breastfeeding mother should be advised to stop breastfeeding.

The duration of stopping will depend on the particular radiolabelled medicinal product.

Further information concerning the use of ^{64}Cu-labelled medicinal products in pregnancy and breastfeeding is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.

Fertility

According to literature reports, it may be considered that both spermatogenetic and genetic damage in male testis are unlikely at the dose of 1GBq.

Further information concerning the effect on fertility of the use of ^{64}Cu-labelled medicinal products is specified in the Summary of Product Characteristics of the medicinal product to be radiolabeled.

2.5.2. Conclusions on the clinical safety

For the purpose of an application for a radiopharmaceutical for radiolabelling, the safety of Cuprymina has been adequately addressed.

2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 1. Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed routine risk minimisation activities
Developmental toxicity including teratogenicity	Routine pharmacovigilance	**SmPC section 4.3**: Established or suspected pregnancy or when pregnancy has not been excluded **SmPC section 4.6**: Women of childbearing potential When an administration of radioactive medicinal products to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient. Before the use of 64Cu-labelled medicinal products, pregnancy should be excluded using an adequate/validated test. Pregnancy The use of 64Cu-labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3).
Neoplasms	Routine pharmacovigilance	**SmPC section 4.8:** The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.
Radiation exposure to other individuals	Routine pharmacovigilance	**SmPC section 4.6**: Breastfeeding Before administering radiopharmaceuticals to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to the choice of the most appropriate

		radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, a breast-feeding mother should be advised to stop breastfeeding. The duration of stopping will depend on the particular radiolabelled medicinal product. **SmPC section 4.2**: Paediatric population 64Cu-labelled medicinal products should not be used in children and adolescents up to 18 years. **SmPC section 4.4**: General warnings Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. **SmPC section 6.6:** General warning Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation. Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken. If at any time in the preparation of this product the integrity of this container is compromised it should not be used. Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory. Healthcare personnel is suggested to limit the time of close contact with patients injected with 64Cu-radiopharmaceuticals. The use of television monitor systems to monitor the patients is recommended. Given the long half-life of 64Cu it is specially recommended to avoid internal

		contamination. For this reason it is mandatory to use protective high quality (latex/nitrile) gloves in any direct contact with the radiopharmaceutical (vial/syringe) and with the patient. For minimising radiation exposure with repeated exposition there is no recommendation except the strict observance of the above ones. The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. **SmPC section 12:** The administration of radioactive medicinal products creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.
Risk in children	Routine Pharmacovigilance	**SmPC section 4.2**: Paediatric population 64Cu-labelled medicinal products should not be used in children and adolescents up to 18 years.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.7. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

3. Benefit-Risk Balance

Benefits-Clinical utility

Cuprymina is a radio-pharmaceutical precursor intended solely for radio-labelling purposes with other medicinal products such as monoclonal antibodies, peptides or other substrates for radio-nuclide therapy. As a precursor, Cuprymina is not to be given directly to patients.

Published experience of ^{64}Cu showed the therapeutic utility in imaging of hypoxia and of tumours sites and metastases. Appropriate information to support an indication as a radio-pharmaceutical precursor for radiolabelling has been provided. Relevant non-clinical and clinical information related to the clinical

use of the carrier molecules, which have been specifically developed and authorised for radio-labelling with this radionuclide, are to be included in the SmPC of the carrier molecules.

Risks

There are no major safety concerns with regards to free Cuprymina as the doses of Cuprymina expected to be administered are unlikely to be associated with toxicity from a copper overload. Moreover, and as for all radioactive products, unfavourable effects relating to the radioactivity would be expected. These include carcinogenicity, mutagenicity, and effects on different tissues. These would be dependent on the radiation characteristics of copper-64 in Cuprymina as well as on the carrier molecule to which Cuprymina is labelled. In addition to radiation exposure to the patient, the risk of radiation exposure to other individuals is also a risk, considering the emission of high energy gamma rays from copper-64. Exposure to ionising radiation must be justified on the basis of likely clinical benefit. However, the radiation safety of Cuprymina in its use as radiopharmaceutical precursor has been demonstrated.

Discussion on the benefit-risk balance

There are no unresolved quality issues, which would have a negative impact on the benefit/risk balance of the product.

No clinical data relevant for the marketing authorisation application of this radiopharmaceutical precursor were submitted. However, sufficient appropriate literature reports on the clinical utility of ^{64}Cu labelled monoclonal antibodies and other ^{64}Cu labelled substrates (^{64}Cu-TETA-OC, ^{64}Cu MAb-1A3, ^{64}Cu ATSM) in humans.

Dosimetry has been calculated from a nude mouse non GLP biodistribution study providing data for the evaluation of human internal radiation dosimetry. Overall, for the purpose of an application for a radiopharmaceutical for radiolabelling, the safety of Cuprymina has been adequately addressed.

In conclusion, a positive benefit/risk balance was demonstrated for Cuprymina in the use only for the radio-labelling of carrier molecules which have been specifically developed and authorised for radio-labelling with this radionuclide. No additional pharmacovigilance activities or additional risk minimisation measures are required other than the information included in the SmPC.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cuprymina as a radiopharmaceutical precursor, not intended for direct use in patients, and to be used only for the radiolabelling of carrier molecules, which have been specifically developed and authorised for radiolabelling with this radionuclide, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that copper (^{64}Cu) chloride is qualified as a new active substance.

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