SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cuprymina 925 MBq/mL radiopharmaceutical precursor, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 925 MBq of copper (^{64}Cu) chloride at calibration time (01h00 a.m. Central European Time [CET]), corresponding to at least 0.25 micrograms of Copper-64. The calibration time is set between the end of the synthesis time and the expiry time.

Each vial contains an activity ranging from 925 MBq to 2,770 MBq (at calibration time) which corresponds to an amount of 0.25 to 0.75 micrograms of Copper-64. The volume varies from 1 to 3 mL.

The minimal specific activity is 3,700 MBq Copper-64/micrograms of Copper at the expiry date and time.
Copper-64 has a half-life of 12.7 hours.
Copper-64 decays by an emission of β^+ (17.6 %) with a maximum energy of 0.66 MeV, an emission of β^- (38.5 %) with a maximum energy of 0.58 MeV and electronic capture (43.9 %).
Copper-64 decays in stable Nickel ^{64}Ni (61 %) by an emission of β^+ (18 %) or by an electronic capture (43 %). Copper-64 decays also in stable Zinc (^{64}Zn) by emission of β^- (39 %).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Radiopharmaceutical precursor, solution.
Clear, colourless solution, free of particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

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

Posology

The quantity of Cuprymina required for radiolabelling and the quantity of Copper-64-labelled medicinal product that is subsequently administered will depend on the medicinal product radiolabelled and its intended use.
Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

Paediatric population

Copper-64-labelled medicinal products should not be used in children and adolescents up to 18 years.
For more information concerning paediatric use of Copper-64-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the radiolabelled medicinal product.

Method of administration

Cuprymina is intended for *in vitro* radiolabelling of medicinal products, which are subsequently administered by the approved route.
Cuprymina should not be administered directly to the patient.
For instruction on preparation of the medicinal product, see section 12.

4.3 Contraindications

- 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 Copper-64-labelled medicinal products prepared by radiolabelling with Cuprymina refer to the Summary of Product Characteristics/package leaflet of each particular medicinal product to be radiolabelled.

4.4 Special warnings and precautions for use

Individual benefit/risk justification

Cuprymina is not to be administered directly to the patient but must be used for the radiolabelling of carrier molecules, such as monoclonal antibodies, peptides or other substrates.

General warnings

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 Copper-64-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 Copper-64 gamma dose constant is 3.6×10^{-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 Copper-64 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 (1 mSv/year).
Special precautions for relatives, carers and hospital staff are provided in section 6.6.

Disappearance of radioactivity

Considering that each MBq of Copper-64 causes a dose rate of 9 nSv/h (at a distance of 2 meters) and that the maximum injected activity is of 2,770 MBq, the initial dose rate is 24,930 nSv/h.
Assuming that the environmental background value is of 150 nSv/h, and requiring that the dose rate due to Copper-64 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 1.

Table 1 – Condition of negligible radioactivity in the patients

	Days after injection (2,770 MBq)	0	1	2	3	4	5
	Dose rate (nSv/h)	24,930	6,727	1,815	490	132	37

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies of Copper-64 chloride with other medicinal products have been performed. The possible use of chelating therapies could interfere with the use of Copper-64-labelled medicinal products. For information concerning interactions associated with the use of Copper-64-labelled medicinal products refer to the Summary of Product Characteristics/package leaflet of the radiolabelled medicinal product.

4.6 Fertility, Pregnancy and lactation

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 Copper-64-labelled medicinal products, pregnancy should be excluded using an adequate/validated test.

Pregnancy

The use of Copper-64-labelled medicinal products is contraindicated during established or suspected pregnancy or when pregnancy has not been excluded (see section 4.3).

Breast-feeding

Before administering radiopharmaceuticals to a mother who is breast-feeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding, 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 breast-feeding.
The duration of stopping will depend on the particular radiolabelled medicinal product.
Further information concerning the use of Copper-64-labelled medicinal products in pregnancy and breast-feeding 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 test is are unlikely at the dose of 1,000 MBq.
Further information concerning the effect on fertility of the use of Copper-64-labelled medicinal products is specified in the Summary of Product Characteristics of the medicinal product to be radiolabelled.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions following the intravenous administration of Copper-64-labelled medicinal products prepared by radiolabelling with Cuprymina, will be dependent on the specific medicinal product being used. Such information is supplied in the Summary of Product Characteristics/package leaflet of the medicinal product to be radiolabelled.
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.

The radiation dose to the patient resulting from exposure after administration 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The presence of free copper (^{64}Cu) chloride in the body after an inadvertent administration of Cuprymina will lead to increased hepatotoxicity.
Therefore, in case of an inadvertent administration of Cuprymina, the radiotoxicity for the patient must be reduced by immediate (i. e. within 1 hour) intravenous administration of preparations containing chelators like Ca-DTPA or Ca-EDTA in order to increase the elimination of the radionuclide from the body.

The following preparations must be available in medical institutions, which use Cuprymina for labelling of carrier molecules:
- Ca-DTPA (Trisodium calcium diethylenetriaminepentaacetate) or
- Ca-EDTA (Calcium disodium ethylenediaminetetraacetate)

These chelating agents help elimination of copper radiotoxicity by an exchange between the calcium ion and the copper due to their capacity of forming water soluble complexes with the chelating ligands (DTPA, EDTA).

These complexes are rapidly eliminated by the kidneys.
1 g of the chelating agents should be administered by slow intravenous injection over 3 – 4 minutes or by infusion (1 g in 100-250 mL of glucose, or sodium chloride 9 mg/mL (0.9 %) solution for injection).
The chelating efficacy is greatest immediately or within one hour of exposure when the radionuclide is circulating in or available to tissue fluids and plasma. However, a post-exposure interval > 1 hour does not preclude the administration and effective action of chelator, even if with reduced efficiency. Intravenous administration should not be protracted over more than 2 hours.

In any case the blood parameters of the patient have to be monitored and the appropriate actions immediately taken if there is evidence of damages.

The toxicity of the free Copper-64 due to *in vivo* release from the labelled biomolecule in the body during therapy could be reduced by post-administration of chelating agents.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: various diagnostic radiopharmaceuticals, ATC code: Not yet assigned

The pharmacodynamic properties of Copper-64-labelled medicinal products prepared by radiolabelling with Cuprymina, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled. Refer to the Summary of Product Characteristics/package leaflet of the particular medicinal product to be radiolabelled.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of the studies with Cuprymina in all subsets of the paediatric population on grounds of lack of significant therapeutic benefit over existing treatments. This waiver does however not extend to any diagnostic or therapeutic uses of the medicinal product when linked to a carrier molecule.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Copper-64-labelled medicinal products prepared by radiolabelling with Cuprymina, prior to administration, will be dependent on the nature of the medicinal product to be radiolabelled.
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 Copper-64-laden blood. Liver, kidney and the intestinal tract reached their maximal content of Copper-64 within the first few hours, and then radioactivity steadily diminished. Part of the decrease can be attributed to excretion of Copper-64 into the bile, urine and faeces.
Blood radioactivity decreased from 60.3 % to 3.4 % after 1 hour, and then it decreased of 1 % after 6 hours, and increased to 5.6 % and 4.9 % after 12-24 hours.
Copper chloride ($^{64}CuCl_2$) 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 $^{64}CuCl_2$ rapidly leaves the blood and enters the liver and kidney.
Maximum liver uptake was 4 hours after injection with 57.7 %. Then copper re-emerges in plasma and is distributed to other organs.

Pharmacokinetic data on Cuprymina relate to free copper

When the precursor is bound to a carrier molecule the content of radioactive free copper is supposed to be less than the stated amounts depending on the carrier used. Relevant data is included in the Summary of Product Characteristics of the labelled medicinal products.

5.3 Preclinical safety data

The toxicological properties of Copper-64-labelled medicinal products prepared by radiolabelling with Cuprymina prior to administration will be dependent on the nature of the medicinal product to be radiolabelled.
No animal toxicity studies were conducted with Cuprymina.
Toxicity of copper compounds has been extensively investigated both in human and in animals. Liver, gastrointestinal tract and kidney are the target organs for copper toxicity after single and repeated doses 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.
Non-clinical data reveal no special hazard for humans based on available published data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (0.1 N).
Water for injections.

6.2 Incompatibilities

Radiolabelling of carrier molecules, such as peptides, monoclonal antibodies, or other substrates, with Copper (^{64}Cu) chloride is very sensitive to the presence of trace metal impurities.
It is important that all glassware, syringe needles etc, used for the preparation of the radiolabelled compound are thoroughly cleaned to ensure freedom from such trace metal impurities. Only syringe needles (for example, non-metallic) with proven resistance to dilute acid should be used to minimise trace metal impurity levels.

6.3 Shelf life

48 hours from date and time of End of Synthesis (EOS).

6.4 Special precautions for storage

Store in the original package that provides protection from radiation.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

The radiopharmaceutical precursor solution is packaged in a colourless, type I glass 10 mL vial, closed with bromobutyl rubber stopper and aluminium overseal.
The volume of one vial ranges from 1 to 3 mL solution (corresponding to 925 to 2,770 MBq at calibration time).
The vials are packed into a tungsten or lead container for protective shielding.
Each pack contains 1 vial in a tungsten or lead container.

6.6 Special precautions for disposal

Cuprymina is not intended for direct use in patients.

Cuprymina is a sterile solution.

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.

For instruction on preparation of the medicinal product, see section 12.
If at any time in the preparation of this medicinal 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. The surface dose rates and the accumulated dose depend on many factors. Measurements on the location and during work are critical and should be practiced for more precise and instructive determination of overall radiation dose to the staff. Healthcare personnel are advised to limit the time of close contact with patients injected with Copper-64-radiopharmaceuticals. The use of television monitor systems to monitor the patients is recommended. Given the long half-life of Copper-64 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. Radiation protection precautions in accordance with national regulations must therefore be taken.

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

7 MARKETING AUTHORISATION HOLDER

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