

Member State EU/EEA	Marketing authorisation holder	Applicant	(Invented) Name	Strength	Pharmaceutical form	Route of administration
Spain		ROTOP Pharmaka AG Bautzner Landstraße 400 D-01328 Dresden Germany	ROTOP-NanoHSA 500 microgramos equipo de reactivos para preparación radiofarmacéutica	0.5 mg	Kit for radiopharmaceutical preparation	Subcutaneous use
Sweden		ROTOP Pharmaka AG Bautzner Landstraße 400 D-01328 Dresden Germany	NanoHSA	0.5 mg	Kit for radiopharmaceutical preparation	Subcutaneous use
United Kingdom		ROTOP Pharmaka AG Bautzner Landstraße 400 D-01328 Dresden Germany	Nanotop	0.5 mg	Kit for radiopharmaceutical preparation	Subcutaneous use, Intravenous use

Annex II

Scientific conclusions and grounds for positive opinion

Scientific conclusions

Overall summary of the scientific evaluation of Nanotop and associated names (see Annex I)

Nanotop is a diagnostic radiopharmaceutical kit containing denatured human serum albumin (HSA), which after radiolabelling with Sodium Pertechnetate (^{99m}Tc) solution results in Technetium (^{99m}Tc) Nanocolloid.

Technetium (^{99m}Tc) Nanocolloid is used for characterisation of the properties of the lymphatic system and in particular sentinel lymph node (SLN) detection in breast cancer and malignant melanoma.

The efficacy of a Tc-99m albumin colloid is the ability to identify the first draining SLN. Once the Tc-99m albumin colloid is administered, the passage of the tracer through the lymphatic system is recorded by imaging.

The mutual recognition marketing authorisation application (MAA) for Nanotop 0.5 mg, kit for radiopharmaceutical preparation / lyophilisate for suspension for injection was submitted on the basis of the marketing authorisation granted by Germany on 8th December 2011. The legal basis for the submitted marketing authorisation application (MAA) was Article 10a "well established use", relying on appropriate scientific literature data of another similar product, Nanocoll.

During the mutual recognition procedure (MRP), major concerns were raised by the member states Sweden and France, that considering the batch variability, it was not possible from a quality perspective to conclude about the comparability between Nanotop and Nanocoll. During the CMDh referral procedure that followed, no consensus could be reached as Sweden maintained their objection that the importance of the batch variability for the distribution and uptake of Nanotop in lymph nodes, as well as its clinical implications had not been adequately addressed, as even a small difference in efficacy could represent a potential serious risk to public health. The CMDh therefore referred the matter to the CHMP through an Art 29(4) referral procedure.

Due to different views in the interpretation of the data related to particle size distribution within the defined limits relevant for efficacy, this referral was triggered to assess the importance of the batch to batch variability for the distribution and uptake of Nanotop in lymph nodes, and whether this could have an impact on efficacy. Since the references included in this submission were studies conducted with Nanocoll, the MAH provided arguments that these data are relevant for Nanotop.

The qualitative and quantitative composition of the medicinal product Nanotop was shown to be the same in comparison to the comparator product Nanocoll.

The upper particle size limits for SLN detection procedures used in Europe has been established and the acceptance criterion of at least 95% of particles having a diameter ≤ 80 nm was shown to be met by all batches of Nanotop. During development the MAH looked into the size distribution below 80 nm and created "particle size groups". Filters at 15 nm, 30 nm, 50 nm and 80 nm filter pore size were used. The particle range of Nanotop corresponds to that of Nanocoll.

In response to the objection that there is a difference in the data fluctuation between Nanotop and Nanocoll, the MAH has provided data to show that the fluctuations observed are comparable and that particle size group distribution is comparable between Nanotop and Nanocoll. The MAH argued that the fluctuations per se are not clinically relevant and therefore differences between such fluctuations are not likely to pose a risk to public health.

In addition the MAH has provided data on Nanocoll and Nanotop batches that were analysed on four days (six batches), and on the same day. The data provided by the MAH support the notion that

variability may decrease when batches are analysed over a shorter period of time. This additional supportive data was considered acceptable by the CHMP to demonstrate that the particles size distribution for the studied size ranges as well as the batch variability is in the same range as for Nanocoll, the product referred to in the submitted literature.

As mentioned previously, the efficacy of a Tc-99m albumin colloid is the ability to identify the first draining SLN. Once the Tc-99m albumin colloid is administered, the passage of the tracer through the lymphatic system is recorded by imaging. If the subcutaneously injected particles are too small they “run” through the lymphatic system too quickly and disappear before imaging techniques can be applied. On the other hand, if the particles are too large they would mostly remain trapped at the injection site and need too much time for transition to the lymph nodes, which is not practical. Based on this, an optimal particle size range has been established for SLN detection.

The MAH has discussed particle size ranges and its implication for clinical practice in general, with reference to clinical guidelines. The relevant quality attributes including upper particle size limits are defined in the European core summary of product characteristics (SmPC) for Tc-99m Albumin Microcolloid (nm), in the relevant European and national Treatment Guidelines^{1,2,3} and in the SmPC of the approved products (e.g. Nanocoll) and have been cited by the MAH. In addition the MAH’s clinical expert states that any variability in particle size within the specified range of Nanotop (≤ 80 nm of at least 95% of the particles) is not relevant for the clinical outcome.

The HSA nanocolloid has the prerogative to be made up of particles smaller than other colloidal agents for SLN detection. The *particle size range* is in this respect the crucial parameter that characterises the particular compound since small-sized colloids allow identification of a greater number of sentinel lymph nodes with a high statistical significance⁴. There have been no studies so far investigating the clinical effects of variability occurring within the particle size range of HSA nanocolloid (of 0 to 80 nm).

Considering the particle size and the particle size ranges range discussed above, the CHMP was of the view that Nanotop is comparable to Nanocoll - the product referred to in the submitted literature, and that therefore an impact on clinical efficacy is not expected.

Grounds for positive opinion

Whereas,

- The Committee considered the notification of the referral triggered by the Germany under Article 29(4) of Directive 2001/83/EC;
- The Committee reviewed the bibliographic data submitted by the marketing authorisation holder to address the potential serious risk to public health with regard to the impact of the observed batch variability on the efficacy of Nanotop in comparison with Nanocoll, which is the product referred to in the submitted literature.
- The Committee was of the view that further analysis of the supportive data from additional batches of Nanotop and Nanocoll have demonstrated acceptably that the particles size distribution for the

¹ Buscombe et al. Sentinel node in breast cancer procedural guidelines. Eur J Nucl Med Mol Imaging (2007) 34:2154.

² Chakera et al. EANM-EORTC general recommendations for sentinel node diagnostics in melanoma. Eur J Nucl Med Mol Imaging (2009) 36:1713.

³ Giammarile et al. The EANM and SNMMI practice guideline for lymphoscintigraphy and sentinel node localization in breast cancer. Eur J Nucl Med Mol Imaging (2013) Oct 2.

⁴ Leidenius MH, et al. The impact of radiopharmaceutical particle size on the visualization and identification of sentinel nodes in breast cancer. Nucl Med Commun 2004;25(3):233-238.

studied size ranges as well as the batch variability for Nanotop is in the same range as for Nanocoll.

- The Committee therefore concluded that the MAH has satisfactorily demonstrated that Nanotop is comparable to Nanocoll, and that therefore an impact on clinical efficacy is not expected.

the CHMP has recommended the granting of the marketing authorisation for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of this Opinion for Nanotop and associated names (see Annex I).