HERMIA

INSTRUCTIONS FOR USE

Voxel Dosimetry

Version 3.1.0

HERMES MEDICAL SOLUTIONS

Document Name: P55-140 Instructions For Use Voxel Dosimetry 3.1.0 Rev.4_EN
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This Instructions For Use (IFU) informs the user of the software's intended purpose, proper use, and any precautions that need to be taken and includes general product information and the information needed to identify the device and its manufacturer.

Any safety and performance information relevant to the user is stated in this IFU and residual risks are described. Study this manual carefully before using the software.

This is an electronic document, a copy of which can be downloaded from www.hermesmedical.com/ifu. Hard copies of Instructions for Use, System Environment Requirements, and Release Notes are available for free (as many as number of purchased licenses) upon request.

This IFU contains WARNINGS concerning the safe use of the product. These must be followed.

This is the general warning sign.

NOTE: A note provides additional information to be aware of, for example, things to consider when performing a certain procedure.

*Subject to registration in some markets

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1 INTRODUCTION

1.1 General notes

Modification of the product is not allowed and may result in hazardous situations.

Only properly trained service personnel by an authorized dealer or by Hermes Medical Solutions shall perform installations, and service of this product.

All users need to be trained, by personnel from an authorized dealer or by Hermes Medical Solutions, in the basic functionalities of the software before use. See list of basic functionalities in *Appendix 1 - User Training Required Content*.

User provided protocols, scripts and programs are not validated nor warranted by Hermes Medical Solutions. The party using such programs is solely responsible for the results.

Hermes Medical Solutions takes no responsibility for loss of data.

The information obtained from using the software shall, in conjunction with other patient related data, as appropriate, be used to inform clinical management. The users of the software are solely responsible for the clinical decisions, such as resulting diagnoses, radiation protection measures or treatments.

The IFU is translated into the local language for countries for which this is a market requirement.

1.2 Regulatory information

Information specific for the EU market
This product complies with Medical Device Regulation (MDR) 2017/745. A copy of the corresponding Declaration of Conformity is available on request.

European SRN number
The single registration number (SRN) = SE-MF-000023032 has been issued to Hermes Medical Solutions AB, as required by the EU MDR – Regulation (EU) 2017/745.

Not available for sale in the USA
Voxel Dosimetry, with the Intended Use as stated in section 2.1 below, is not available on the US market. For the US IFU and intended use, please see P55-174 US Instructions For Use Voxel Dosimetry 3.1.0.

Canada - the Device identifier, as defined with Health Canada, is the first two numbers in the version number.

1.3 Associated documentation

- P55-148 Release Notes Voxel Dosimetry 3.1.0 Rev.4
- PC-007 System Environment Requirements, applicable revision can be found at www.hermesmedical.com/ifu.

A user guidance, intended to assist users in using the software, is available from the Help function in the software itself.

2 PRODUCT INFORMATION

2.1 Intended purpose

Intended Use
Voxel Dosimetry is a software application for nuclear medicine. Based on user input of nuclear medicine image data, Voxel Dosimetry calculates a volumetric map of the distribution of absorbed radiation dose (a dose map) on the voxel level and presents the results to the user. The result can be stored for future analysis.

Voxel Dosimetry can calculate the predicted dose map of a different radionuclide or different injected activity based on an image of the first measured radionuclide. The dose distribution estimated by Voxel Dosimetry may guide the decision making for future patient radionuclide therapy treatments or inform radiation protection measures for diagnostic radiopharmaceuticals.

The software application can be configured based on user needs.

Intended User
The intended users of Voxel Dosimetry are medical professionals trained in using the system.

2.2 Intended patient population and medical conditions

Patients of any age and gender undergoing radionuclide therapy.

Intended medical indication is any for which radionuclide therapy is performed. Common clinical areas include but are not limited to: oncology, for example treatment of neuroendocrine tumors with Lu-177 DOTA-peptides; and endocrinology, for example treatment of hyperthyroidism with I-131 iodide.

2.3 Contraindications

There are no contraindications.

2.4 Product label

The version number, the Unique Device Identification (UDI) and other product data of an installed Voxel Dosimetry 3.1 software can be found by clicking on the information symbol ⓘ at top right of the application window to open the ‘About Box’.

The following information can be identified:
Product name = Voxel Dosimetry
Release version = 3.1.0
Marketing name = Hermia Voxel Dosimetry
Software build no = 43

℞ Only	Prescription only” - device restricted to use by or on the order of a physician
	Date of Manufacture (YYYY-MM-DD)
UDI	Unique Device Identification number
MD	Indicates that the product is a medical device

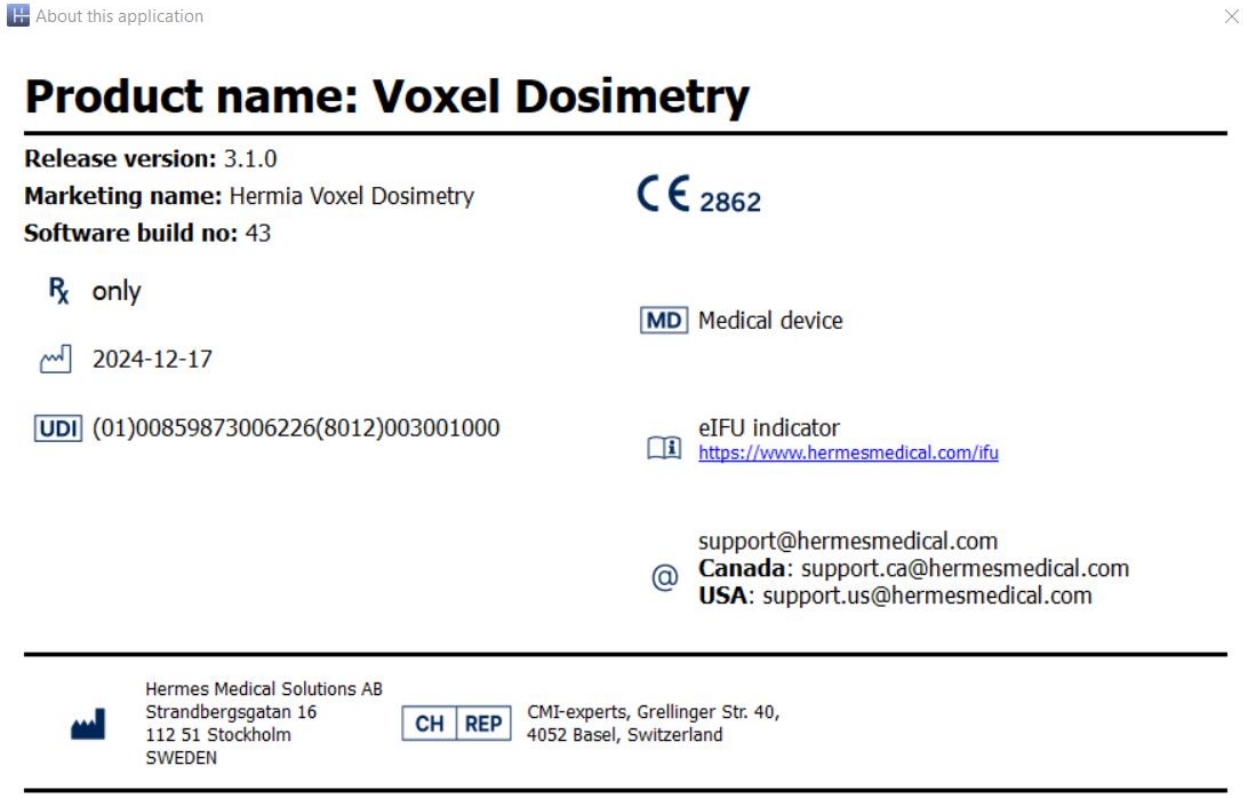
CE 2862 CE marking and the Notified Body number

Consult Instructions for Use (IFU)

@ The support email addresses

Manufacturer's contact information

CH REP Swiss authorized representative



2.5 Product Lifetime

The lifetime of Voxel Dosimetry 3.1 is 5 years.

The lifetime of 5 years starts running when Voxel Dosimetry 3.1 has been manufactured (5 years from Manufacturing date of 3.1.0). Possible patches on Voxel Dosimetry 3.1 will have new manufacturing dates, but the lifetime will not start over from manufacturing of a patch.

During the stated lifetime, Hermes Medical Solutions maintains the safety and performance of Voxel Dosimetry. Patches are provided if necessary to maintain the safety and performance of the product.

2.6 Complaints and serious incidents

Report incidents and errors to our support, see *Contact Information*.

Any serious incident that has occurred in relation to the device must be reported to the manufacturer.

Depending on applicable regulations, incidents may also need to be reported to national authorities. For the European Union, serious incidents must be reported to the competent authority of the European Union Member State in which the user and/or patient is established.

Hermes Medical Solutions welcomes feedback from readers of this manual, please report any errors in content or typography and suggestions for improvements to our support, see *Contact Information*.

2.7 Hardware and Operation systems

For general requirements, see *PC-007 System Environment Requirements*.

No other than Hermes Medical Solutions approved applications shall be installed on the computer device for which Hermes Medical Solutions software are intended to be used. Use of other applications may result in impaired performance and, in the worst case, incorrect output data.

2.8 Interoperability with Hybrid Viewer and Affinity

Voxel Dosimetry is interoperable with Hybrid Viewer, version 4.0 or later. Hybrid Viewer versions prior to version 4.0 do not have the functionality to display a Dose map.
Voxel Dosimetry is interoperable with Affinity, version 4.0 or later.

2.9 Installation

Installation must comply with applicable requirements such as, but not limited to, system requirements, configuration, and licensing.

2.9.1 Warnings

NOTE: Adding radionuclides that have not been validated is a modification of the product. For validated radionuclides, see *Appendix 3 List of supported isotopes.*

Modification of the product is not allowed and may result in hazardous situations.

Only properly trained service personnel by an authorized dealer or by Hermes Medical Solutions, shall perform installations, and service of this product.

User provided protocols, scripts and programs are not validated nor warranted by Hermes Medical Solutions. The party using such programs is solely responsible for the results.

No other, than Hermes Medical Solutions approved, applications shall be installed on the computer device for which Hermes Medical Solutions applications are intended to be used. Use of other applications may result in impaired performance and, in the worst case, incorrect output data.

3 SAFETY AND PERFORMANCE INFORMATION

3.1 Definitions

Following definitions are used in this document.

3D	Three dimensional
CT	Computed Tomography
DVH	Dose-Volume Histogram
GPU	Graphics processing unit
HU	Hounsfield Units
PET	Positron Emission Tomography
ROI	Region Of Interest
SPECT	Single Photon Emission Computed Tomography
TAC	Time-activity curve
VOI	Volume Of Interest

3.2 Summary

Voxel Dosimetry is an application for SPECT or PET-based 3D voxel level dosimetry. Voxel Dosimetry can be used with between 1 and 10 SPECT or PET datasets with 1 CT study or with as many CTs as there are emission studies.

Voxel Dosimetry calculates voxel level absorbed doses in three steps.

In the first step all the time points are aligned to a reference study. Image registration works either by registering a time-sequence of CT images to a common reference or by registering SPECT/PET images. Mutual information-based registration algorithm is used. In addition to rigid registration, non-rigid registration using the Demons-algorithm is available for CT to CT registrations.

In the second step TACs for each voxel are first generated and then integrated. The TAC generation can be performed either on voxel or organ level. In the case of voxel level TACs, the TAC for each voxel is generated and integrated depending on the various options available. These options are explained in more detail in the next section. In the case of organ level TACs, organ (or lesion) VOIs are first drawn manually or by using an automatic algorithm. The TACs are then fitted with mono-exponential or bi-exponential functions. The same organ level TAC-shape is used for all voxels inside the VOI and the TAC is integrated analytically. Voxels outside the segmented VOIs will be grouped into a 'remainder of body' VOI, which will have its own distinct curve.

In the third step the dose calculation is performed. The dose calculation algorithm is independent of the TAC type.

Finally, the generated dose map will be shown. If organ or lesion VOIs were drawn, tabulated dose values and dose volume histograms can also be shown and be copied for further analysis. The generated dose map can be saved together with the segmentation files and can optionally be loaded into an external application, such as Affinity or Hybrid Viewer.

3.3 Workflow

Select reconstructed SPECT or PET datasets and corresponding CTs. If you have DICOM segmentations attached to one of the CTs you can load those too. Select the "**Voxel Dosimetry**" application to launch the application.

The Voxel Dosimetry workflow consists of alignment, VOI drawing, dose calculation and result viewing steps. All these steps have a pushbutton ("**Align**", "**VOI**", "**Dose**" and "**Results**") in the user interface.

For multiple time point studies, the first step is to align all time points to the reference study which was selected when loading data. For single time point studies, registration is not needed and registration controls are inactive.

The Align page is shown in **Figure 1**. Alignment is performed by registering SPECT/PET or CT images. The registration mode is selected by clicking either the "**SPECT/PET**" or "**CT**" radio button. The data corresponding to a certain time point can be viewed and aligned by selecting it from the "**Dataset**" dropdown menu. The image data is displayed overlaid on the reference image to allow visual assessment of alignment.

Color table controls can be found below the images.

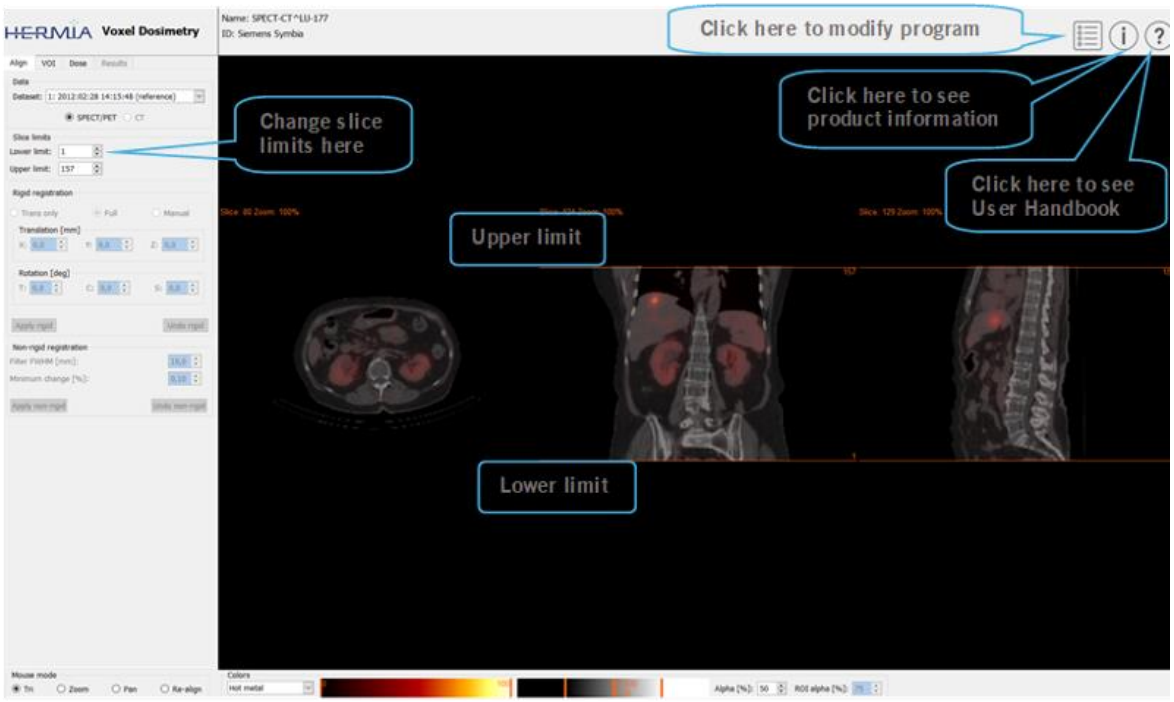


Figure 1. Time-point alignment page

After all images have been aligned, the "**VOI**" and "**Dose**" tabs become active. VOI drawing is optional, but VOIs must be used if organ level TAC fitting is required, or if you wish to review organ level dose results in Voxel Dosimetry rather than in an external DICOM viewer. The VOI tab is shown in **Figure 2**. If you have loaded DICOM segmentations, they will be visible here.

The organ regions may be created automatically; kidney, liver, spleen, and lung organ models are available. Select the organs using the tick boxes and click the "**Segment organs**" button. VOI numbers and names are automatically assigned. All organ regions should be checked carefully by scrolling through the C, T and S slices.

Automatic lesion segmentation can be performed by using Thresholding or Fuzzy C-Means, selectable from the "**Method**" dropdown menu. Both operations are performed within a constrained region set by the user.

Before applying a segmentation constraint to the NM image, the user should first establish the extent of the lesion by triangulating to it and scrolling, then placing a bounding box over the relevant volume. The bounding box for lesion segmentation is first set by pressing the “**Bounding Box**” button and left clicking the lesion center. The size of the box can be changed by clicking and dragging the handles at the edges and the position by moving the central cross with the left mouse button set. The user is not able to scroll through slices at this point. When the bounding box is correctly placed, click the “**Segment**” button to perform the segmentation. The “**Delete box**” button deletes the bounding box.

After all required VOIs have been created, click the "**Dose**" tab to continue with the dose calculation.

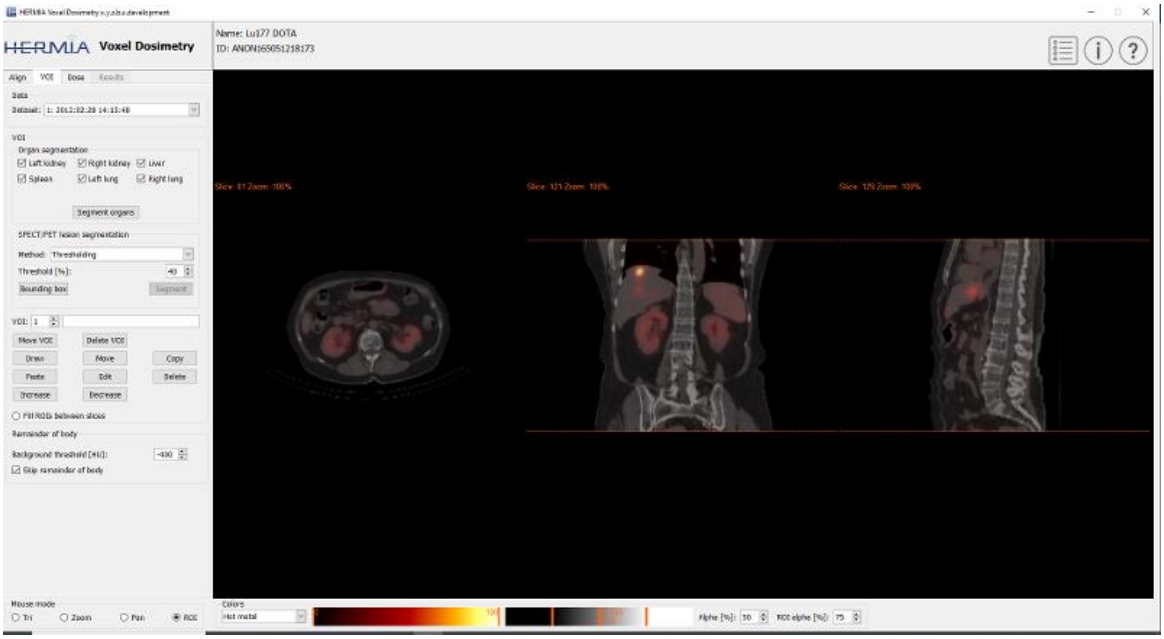


Figure 2. VOI drawing page

The dose calculation page is shown in **Figures 3** and **4**. The simulation protocol can be changed using the "**Simulation protocol**" combobox and the protocol can be viewed by pressing the "**Show protocol**" button. Voxel level or Organ level dosimetry calculation method can be selected, VOIs must have been created in the previous step for Organ level dosimetry to be available. Remainder of body region will be created automatically when Dose tab is selected.

Figure 3. Dose calculation page, voxel level dosimetry.

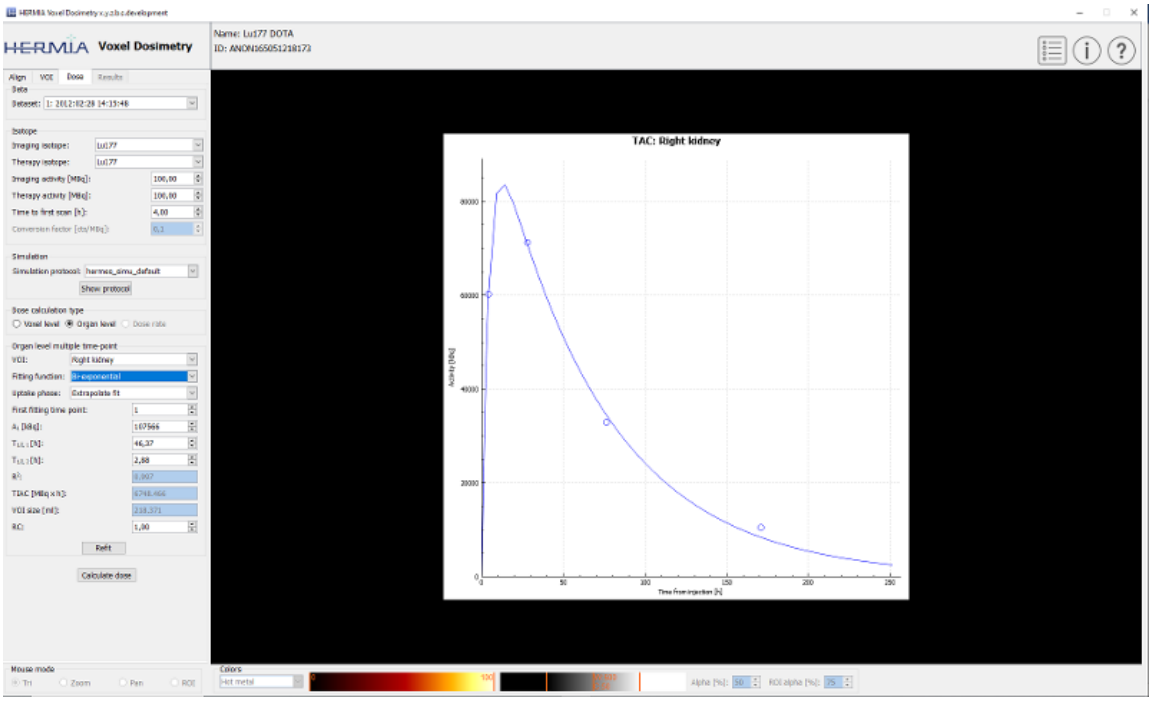


Figure 4. Dose calculation page, organ level dosimetry.

If the T1/2 values (T1/2 1 for mono-exponential and T1/2 1 and/or T1/2 2 for bi-exponential) are changed such that the value of the y-axis scaling factor (A1) is larger than 1.5 times the original value, a pop-up warning message will appear. Either click on the "**Refit**" button or adjust the fit parameters until the y-axis scaling factor (A1) is smaller than 1.5 times the original value.

3.3.1 Results

The Results page (**Figure 5**) displays the dose map ("**Dose map**" radio button) and, if VOIs were drawn, the tabulated dose values ("**Table**" radio button) or cumulative dose-volume histograms

("**DVH**" radio button). The VOIs can be displayed superimposed on the Dose map by clicking the "**Show VOI**" radio button. The VOI displayed in the DVH can be selected from the "**DVH**" dropdown menu. Results table and DVH's can be saved in Results tab for further analysis.
Screen captures can be created using the "**Screen capture**" button. Screen captures will be saved in the database with user defined name and can be viewed with Hybrid Viewer.

The created dose map together with the segmentations can be viewed in external Hermes DICOM viewing applications Affinity or Hybrid Viewer by pressing the "**Launch viewer**" button. If VOIs are saved in results page, they will be transferred to the external viewer when viewer is launched. The viewer to be used can be selected in the "**Program Parameters Results**" tab.

The dose map can be saved to the patient database by pressing the "**Save dose map**" button. If the "**Save VOI**" button is ticked, the drawn VOIs are also saved as DICOM segmentations.

Figure 5. Results page

3.4 Settings

General settings for Voxel Dosimetry can be selected and saved in the Program Parameters window using the six tabs: Launch; Color; Align; VOI; Dose; Results.

3.5 Security

Voxel Dosimetry processes Personal Identifiable Information (PII), so Hermes Medical Solutions actively works with cybersecurity during manufacturing to ensure the highest level of security. To increase security further, the software supports customers' own security measures, such as, but not limited to, access control and authorization, antivirus, operating system patching, and disk encryption. For more information, please contact support@hermesmedical.com.

It is the responsibility of the customer to install and maintain anti-virus software on the server and client computers and apply the necessary protection against threats.

Backup copies of all user and layout protocols supplied with Voxel Dosimetry are stored separately at installation so that the user can revert if required.

Any detected, or suspected, cyber security incident that has occurred with the product must be reported to our support, see Contact Information.

In case Hermes Medical Solutions identify a security issue in our product, Field Security Notices will be issued to all potentially affected customers. The notice will contain detailed instructions on how the users should respond and act to recover from any issue taken place and minimize the risk of being affected by the identified issue.

Depending on applicable regulations, incidents may also need to be reported to national authorities.

The product executable is signed with *Hermes Medical Solutions Aktiebolag*'s Digital Signature to ensure the authenticity and integrity.

In case of network unavailability, starting the product or loading/saving data may fail.
In case the network fails during use of the product, the user should re-load and verify that the saved data is complete. If not, the data should be processed again.

4 WARNINGS

NOTE: Adding radionuclides that have not been validated is a modification of the product.

If the network is unavailable it may not be possible to maintain the Intended Use of the device.

Check the isotope, injection time and injected activity are set correctly as it may not always be possible for the application to obtain this information automatically from the study header.

Verify that the correct reference study was used to calculate the dose map. Errors can cause misrepresentation of the dose maps and result in incorrect treatment of the patient.

Decimal numbers should be entered using a point or comma depending on the Windows Locale setting. If an inappropriate separator is entered it will be removed automatically, so care should be taken to use this correctly.

The image registration should always be checked to ensure it is optimal, before proceeding to the next step. Incorrect registration can lead to misrepresentation of the dose map and incorrect treatment of patients.

All region segmentations must be carefully checked by scrolling through all image slices before dose calculation.

Voxel Dosimetry will modify loaded DICOM segmentations which contain holes, so that they no longer contain holes. Loaded segmentations must be carefully checked by scrolling through all image slices before dose calculation.

When applying recovery coefficients, accuracy is low for volumes smaller than 50 mL and recovery coefficients smaller than 0.7. Care must be taken comparing mean dose for regions created in Voxel Dosimetry and then loaded into other applications. Differences in region quantitation for voxels on the region boundary may result in significant mean dose differences, especially for small regions with small recovery coefficients.

Volumes of regions viewed in Voxel Dosimetry may not perfectly match those displayed in external DICOM viewing applications for the same region. This is due to differences in the voxel grid used to define segmentations in different applications, and quantitation methods for voxels on region boundaries. This may affect dose map region statistics which use all region voxels, for example mean dose, especially for smaller regions.

The information acquired from the dose map should always be used in conjunction with other relevant information when planning treatment.

If manually entering a count to activity conversion factor for SPECT data, dose results must be carefully checked to ensure accuracy.

Fit quality might be compromised. Re-check fitting parameters.

5 CONTACT INFORMATION

Contact any of the addresses below for service, support or if you have any other questions.

5.1 Manufacturer contact information

Head office
Hermes Medical Solutions AB
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112 51 Stockholm
SWEDEN
Tel: +46 (0) 819 03 25
www.hermesmedical.com

General e-mail address:
info@hermesmedical.com

Support e-mail addresses:
support@hermesmedical.com
support.ca@hermesmedical.com
support.us@hermesmedical.com

5.2 Representatives

Authorized representatives

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Cardinal House
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CH Authorized Representative CH REP
CMI-experts
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Switzerland

5.3 Subsidiaries

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6 APPENDIX

6.1 Appendix 1 - User Training Required Content

Launch

- About box and link to IFUs
- User Handbooks
- Data selection (Up to 10 quantitative SPECT or PET and accompanying CTs), possibility to load regions in DICOM SEG format

User interface

- Layout of the application window
- Color table options and adjusting the values for the current session

Workflow

- Data selection and choosing a reference study, see Launch.
- Image alignment of all time points to reference study (CT to CT, SPECT to SPECT or PET to PET)
- Rigid registration (translation, full and manual) and non-rigid registration (only CT to CT)
- Adjusting slice limits during registrations, same limits will be applied to registration, segmentation and dose calculations
- Mouse mode selection
- Region drawing tools including automatic organ segmentation (kidney, liver, spleen, and lung organ models are available, verify that auto segmentation is appropriate/edit regions manually)
- Imaging and therapy isotope selection
- Isotope information
- Simulation protocol selection and adjustments to simulation parameters
- Single time point and multiple time point options
- Differences between Organ and Voxel level dose calculations
- Voxel level time-activity curve calculation options
- Organ level time-activity curve fitting

Saving and displaying Dose map

- Dose map and regions saving options
- Results review in Voxel Dosimetry
- Copying results table and DVH
- Displaying results in Affinity or Hybrid Viewer

Settings

- Program parameters window
- Changing default settings for the application
- Launch settings for labelling and monitor used to launch the application
- Color table options, setting optimal windowing for the studies
- Alignment options, possibility to automate
- VOI drawing options, possibility to automate
- Dose calculation options, possibility to automate
- Results table options and settings for external application launch for dose map display
- Saving changed settings

NOTE: Adding radionuclides that have not been validated is a modification of the product.

6.2 Appendix 2 - Messages from the application

Information Messages with "OK and continue"

- Interfile should only be used for testing.
- Studies have not been co-registered. Cannot proceed until all studies have been registered.
- Time to first scan must not be 0.
- Cannot find isotope information from the study header.
- Problems with simulation protocol.
- Please verify and save the simulation protocol first.
- Error saving dose map.
- Saving failed.
- Cannot launch viewer. Executable cannot be found.
- Make sure the previous viewer has completed loading.
- Default simulation protocol is missing and no replacement can be found. Contact Hermes Medical Solutions for help.
- The simulation protocol path filename does not exists.
- The viewer path does not exist.

Information Messages with "OK"

- Fit quality might be compromised. Re-check fitting parameters
- Automatic dosimetry is available only when emission study is in Bq/ml units. Automatic dose calculation was turned off.
- Automatic dose calculation cannot be performed without automatic alignment. Automatic alignment was enabled.
- Automatic dose calculation is possible only with automatic alignment. Automatic dose calculation was turned off.
- Automatic single time-point dosimetry is possible only with physical half-life and Hanscheid approximation. Automatic dose calculation was turned off
- Effective half-life cannot be longer than physical half-life. Fit has been replaced with physical decay

Information Messages with "OK to continue" or "Abort to abort"

- Only one CT has been loaded. Press OK to continue with one CT or Abort to abort.
- Acquisition time differs xx.yy hh:mm. Please check carefully that correct studies were selected.
- Patient name or IDs do not match in all studies. Press OK to continue with one CT or Abort to abort.
- Deformable registration will only be performed using the data between the upper and lower limit. Press OK to continue, Abort to abort.
- Same or missing frame of reference in emission studies. CT and emission studies will be matched based on time difference. Press OK to continue or Abort to abort.
- Emission study pixel units are not Bq/ml or Bq/cc. If you want to proceed and set counts to activity conversion factor manually press OK otherwise press Abort.

Information message with Yes/No

- Have you set effective half life for every organ? Yes/No

⚠Warning Messages

- Activity and time to first scan values might not have been correctly updated (still set to default values). Press OK to continue with these values or Abort to change them.
- Files have not been saved. Press OK to quit without saving or Abort to abort.

- Counts to activity conversion factor might be wrong.
- Fit quality might be compromised. Re-check fitting parameters.
- Time activity curve cannot be an increasing function. Fit has been replaced with physical decay.
- Scaling factor cannot be negative. Fit has been replaced with physical decay.
- Effective half-life cannot be longer than physical half life. Fit has been replaced with physical decay.

6.3 Appendix 3 - List of supported isotopes

- Gallium-68 / Ga68
- Indium-111 / In111
- Iodine-123 / I123
- Iodine-131 / I131
- Lutetium-177 /Lu177
- Technetium-99m /Tc99m
- Yttrium-90 /Y90
- Holmium-166 /Ho166
- Radium-223 /Ra223
- Zirconium-89 /Zr89
- Fluorine-18 / F18
- Lead-203 / Pb203
- Lead- 12 / Pb212
- Iodine-124 /I124
- Actinium-225 /Ac225
- Astatine-211/At211