THERANOVA 400
500

INSTRUCTIONS FOR USE

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Definition of symbols

	Explanation of non-harmonized symbols	**Warning:** Do not use in Hemodiafiltration or Hemofiltration mode

Symbols are referenced from ISO 15223-1 Medical Devices: Symbols to be used with medical device labels, labeling and information to be supplied - Part 1: General Requirements

Symbol and Symbol Number	Symbol Title	Description
 5.1.1	Manufacturer	Indicates the medical device manufacturer, i.e. the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name.
 5.1.3	Date of Manufacture	Indicates the date when the medical device was manufactured. Format should be YYYY-MM-DD.
 5.1.4	Use-by-date	Indicates the date after which the medical device is not to be used. Format should be YYYY-MM-DD.
 5.1.5	Batch code	Indicates the manufacturer's batch code. Synonyms are "lot number" and "batch number".
 5.1.6	Catalogue number	Indicates the manufacturer's catalog number. Synonyms are "reference number" and "reorder number".
 5.2.5 & 5.2.9	Sterile fluid path; sterilized using steam or dry heat	Indicates the presence of a sterile fluid path within the medical device in cases when other parts of the medical device, including the exterior, might not be supplied sterile. Indicates a medical device that has been sterilized using steam or dry heat.
 5.6.3	Non-pyrogenic	Indicates a medical device that is non-pyrogenic.
 5.4.4	Caution	Indicates the need for the user to consult the instructions for use for important cautionary information such as warnings and precautions that cannot, for a variety of reasons, be presented on the medical device itself.
 5.3.6	Upper limit of temperature	Indicates the upper limit of temperature to which the medical device can be safely exposed.
 5.4.2	Do not re use	Indicates a medical device that is intended for one use, or for use on a single patient during a single procedure. Synonyms for "Do not re-use" are "single use" and "use only once".
 5.4.3	Consult instructions for use	Indicates the need for the user to consult the instructions for use. Synonym for "Consult instructions for use" is "Consult operating instructions".

General Information

Intended Use / Indications for use

Intended Use: To treat chronic kidney failure

Indications for Use: The Theranova Dialyzer is indicated for patients with chronic kidney failure who are prescribed intermittent hemodialysis. It provides an expanded solute removal profile with increased removal of various middle molecules (up to 45 kDa) that may play a pathologic role in the uremic clinical syndrome. The Theranova Dialyzer is not intended for hemofiltration or hemodiafiltration therapy. The total extracorporeal blood volume for the Theranova Dialyzer and the set should represent less than 10% of the patient's blood volume.

Device Description

Device with sterile and non-pyrogenic fluid pathways.

Expanded hemodialysis, enabled by the Theranova dialyzer, expands the range of molecules (up to 45 kDa) efficiently removed during intermittent hemodialysis. Theranova dialyzers provide increased removal of various conventional middle molecules (500 Da to <25 kDa) and large middle molecules (25 kDa to 45 kDa) compared to high flux membranes. See the Performance Section of this IFU for additional data.

Expanded hemodialysis, enabled by the Theranova dialyzer, achieves its performance using existing hemodialysis workflow and infrastructure [1]. See Directions for Use Section.

[1] Kirsch AH, et al. Performance of hemodialysis with novel medium cut-off dialyzers. Nephrol Dial Transplant 2017; 32(1):165-72.

Contraindications

There are no known contraindications for the use of Theranova dialyzers.

Definition of Expressions used in this manual

WARNING! is used to alert the operator not to take a specific action that can cause potential hazard which, if ignored, can result in an adverse reaction, injury or death.

CAUTION! is used to alert the operator to take a specific action to protect against a possible hazard which, if ignored, could have an adverse effect on the patient or equipment.

NOTE! is used to remind the operator of normal treatment functions and what is the suitable action in a particular situation.

General Warnings and Cautions

The dialyzers are for single use only. The quality of the product is guaranteed for first use only, and only when prepared and used according to the procedures described. Reprocessing this dialyzer may cause serious damage to the product resulting in patient hazard.

WARNING! Treatment parameters should be chosen within the limitations given in the specification table.

WARNING! Use the dialyzers only with dialysis equipment which can accurately control and monitor the ultrafiltration rate, and blood in the dialysate circuit (blood leak detector).

WARNING! Expanded removal of molecules up to 45 kDa may lead to increased removal of certain drugs. Clinicians should consider this when prescribing the device and make any necessary dosing adjustments.

WARNING! Expanded removal of molecules up to 45 kDa may lead to increased removal of essential proteins in this size range. Clinicians should consider this possibility when prescribing the device for expanded solute removal.

CAUTION! Federal law (USA) restricts this device to sale by or on the order of a physician.

CAUTION! Do not apply isolated/sequential ultrafiltration when using Theranova dialyzers, due to higher permeability for larger plasma proteins such as free hemoglobin. In dialysis patients plasma free hemoglobin is usually present in low concentrations (up to 239 mg/L [2]). During isolated/sequential ultrafiltration free hemoglobin is filtered and concentrated in the dialysate compartment. This leads to a reddish coloration of the ultrafiltrate which may trigger the internal blood leak detector. [2] Meyer et al., Hemodialysis-induced release of hemoglobin limits nitric oxide bioavailability and impairs vascular function, J Am Coll Cardiol. 2010 Feb. 2;55(5):454-9

Adverse events

Certain types of adverse reactions may occur due to operational factors associated with the treatment.

WARNING! Selection of a suitable dialyzer configuration and of treatment parameters should be considered based on patient characteristics (body size, weight, cardiovascular status, therapy tolerance etc.) and clinical requirements.

WARNING! Adherence to set-up and priming procedures, proper management of fluid removal, electrolyte balance, adjustment of the pH-value of the dialysate, anticoagulation, blood and dialysate flow rates as well as monitoring of the overall treatment parameters are essential to avoid side effects which may be associated with Hemodialysis.

WARNING! Water and dialysate should comply to quality standards such as ANSI/AAMI RD62 or ISO 23500 series. Failure to monitor and maintain water and dialysate quality may result in patient exposure to levels of bacterial or endotoxin contamination capable of causing infection and/or pyrogenic reactions.

In rare cases (e.g. for patients having a history of being highly sensitive to a variety of substances), hypersensitivity reactions may occur during dialysis, particularly at the onset of treatment. In severe cases, dialysis must be discontinued and appropriate medical intervention administered.

After priming the dialysate compartment the fluid in the blood compartment may contain bicarbonate. During patient connection the volume and rate of infusion of this fluid needs to be considered, especially for patients with metabolic acidosis. Discard as much as possible of the priming solution.

Clinical side effects

If an internal blood leak is observed, the operator must stop the treatment session and replace the dialyzer. Do not return the blood to the patient since it may have become contaminated by the dialysis fluid. If necessary, administer adequate replacement solution to the patient to compensate for the blood loss.

WARNING! If an external blood leak is observed, secure connections or replace the dialyzer. If necessary, administer adequate replacement solution to the patient to compensate for the blood loss.

WARNING! If a dialysate compartment leak is observed the operator has to check the correct placement of the dialysate connectors or to stop the treatment and replace the dialyzer. If necessary, administer adequate replacement solution to the patient to compensate fluid imbalance.

WARNING! If air enters the extracorporeal blood circuit, an air embolism may occur. This can be hazardous to the patient. To minimize the risk of air embolism constant monitoring of the extracorporeal blood circuit, both visually and with an air detector, is recommended. Strict adherence to the manufacturer's recommended activities will facilitate the removal and prevent the accumulation of air in the dialyzer before the treatment session. If air enters or is identified in the dialyzer during priming and cannot be removed with the use of additional priming, the dialyzer must be replaced.

CAUTION! If clotting occurs in the dialyzer both the dialyzer and the blood lines must be replaced. Flush the vascular access devices according to clinic procedure. Discard the dialyzer and the blood lines. Do not return the blood to the patient.

Warranty

The manufacturer warrants that the capillary dialyzer has been manufactured in accordance with its specifications and in compliance with good manufacturing practices, other applicable industry standards and regulatory requirements.

If provided with the lot number of the defective product, the manufacturer will, by replacement or credit, remedy manufacturing defects in the dialyzer becoming apparent before the expiry date.

Expiry date: Refer to information on the unit container label.

The warranty above is in lieu of, and to the exclusion of, any other warranty, whether written or oral, expressed or implied, statutory or otherwise, and there are no warranties of merchantability or fitness or other warranties, which extend beyond those described.

The remedy set out above for manufacturing defects is the sole remedy available to any person due to defects in the dialyzer and the manufacturer shall not be liable for any consequential or incidental loss, damage, injury or expense arising directly or indirectly from the use of the dialyzer, whether as a result of any defect therein or otherwise.

The manufacturer shall not be liable for any misuse, improper handling, non-compliance with warnings, directions and instructions in the labeling, damage arising from events after the manufacturer's release of the dialyzer before use in order to insure that the dialyzer is in proper condition, or any warranty given by independent distributors or dealers.

Performance Data

Performance data calculated from values measured according to ISO 8637-1

The performance values given below should be regarded as approximate. Under clinical conditions, different values may be obtained due to the clinical settings and measuring technique.

Information about test methods used to obtain performance data is available from the manufacturer upon request.

PERFORMANCE TABLES SEE SECTION: PERFORMANCES.

Directions for Use

Set-up instructions

WARNING! Do not use if package or product is damaged or if protection caps are not in place.

WARNING! Aseptic technique is required throughout dialysis preparations and treatment to avoid contamination.

WARNING! For automated priming modes please refer to the clinic's protocol and the operator's manual of the dialysis equipment in use.

Recommendations for manual priming:

- Prepare and connect a bag with isotonic saline (e.g. 0.5 L) to the blood lines.
- Remove the protective caps from the blood ports and use them to close the dialysate ports.
- Position the filter vertically and connect the blood lines to the filter to fill up the blood compartment from bottom to top.
- Start the blood pump at 100 mL/min.
- Prime the circuit with ≥ 300 mL isotonic saline.
  WARNING! Eliminate as much air as possible from the blood compartment.
- Attach the dialysate tubing for counter current flow.
- Activate the dialysate flow and remove air from the dialysate compartment of the dialyzer.
- The dialyzer is now ready for connecting to the patient!

Treatment instructions

- Follow instructions in the operator's manual of the dialysis equipment in use.

CAUTION! Anticoagulation is recommended to prevent clotting in the extracorporeal circuit. Anticoagulation therapy should be selected adjusted to the needs of the patient and monitored under the direction of a physician.

If Heparin is used, it is recommended to administer a loading dose to the patient 2 to 5 minutes before start of the treatment.

- Connect the arterial blood line to the vascular access of the patient.
- Connect the venous line to the vascular access of the patient.
- Start the blood pump and increase the blood flow rate to the prescribed value.

To avoid hemoconcentration in the dialyzer, do not start ultrafiltration before desired blood flow rate is reached.

Termination of Treatment

- Follow instructions in the operator's manual of the dialysis equipment in use.
- Connect the arterial blood line to a bag of isotonic saline solution and adjust the blood flow rate to return the blood to the patient.

  This does not apply if online-fluid is used for rinse back.

WARNING! Do not deactivate the air detection system on the machine until the patient is disconnected.

- When the required amount of blood has been returned to the patient, stop the blood pump and disconnect the patient.
- Follow the instructions in the operator's manual of the dialysis equipment in use how to empty and disconnect the dialyzer and blood lines.
- After use, this product may be a potential hazard. Handle and dispose of in accordance with accepted medical practice and applicable local, state and federal laws and regulations.

Performances

Specifications

	REF	Theranova 400	Theranova 500
1	Blood Flow rate: Q_b (mL/min)	200 – 600	200 – 600
2	Dialysate Flow rate: Q_d (mL/min)	300 – 800	300 – 800
3	Surface Area (m^2)	1.7	2.0
4	UFC [mL/(h·mmHg)]	48	59
5	Blood compartment pressure drop (mmHg) (Bovine blood, Hct 32 %, Pct 60 g/L, 37 °C) Q_b = 200 mL/min Q_b = 300 mL/min Q_b = 400 mL/min Q_b = 500 mL/min Q_b = 600 mL/min	 ≤ 90 ≤ 130 ≤ 170 ≤ 210 ≤ 250	 ≤ 80 ≤ 120 ≤ 160 ≤ 200 ≤ 240
6	Dialysate compartment pressure drop (mmHg) Q_d = 300 mL/min Q_d = 500 mL/min Q_d = 800 mL/min	 ≤ 20 ≤ 30 ≤ 50	 ≤ 15 ≤ 25 ≤ 40
7	Blood compartment volume (mL)	91	105
8	Residual blood volume (mL)	< 1	< 1
9	Fluid volume needed for priming (mL)	≥ 300	≥ 300
10	Maximum TMP (mmHg)	600	600
11	Sterilization agent	Steam	Steam
12	Membrane material	Polyarylethersulfone / Polyvinylpyrrolidone (PAES / PVP)	Polyarylethersulfone / Polyvinylpyrrolidone (PAES / PVP)
13	Housing / header material	Polycarbonate (PC)	Polycarbonate (PC)
14	Gasket material	Silicone rubber (SIR)	Silicone rubber (SIR)
15	Potting material	Polyurethane (PUR)	Polyurethane (PUR)
16	Recommended connectors for dialysate ports	Acc. to ISO 8637-1	Acc. to ISO 8637-1
17	Recommended connectors for blood ports	Acc. to ISO 8637-1	Acc. to ISO 8637-1
18	Storage conditions	< 30 °C / 86 °F	< 30 °C / 86 °F

19 - Clearance (mL/min) (± 10 %, Cytochrome C ± 20 %, Myoglobin ± 30 %)

Theranova 400

UF = 0 mL/min		Q_d = 300 mL/min					Q_d = 500 mL/min					Q_d = 800 mL/min				
Q_b (mL/min)		200	300	400	500	600	200	300	400	500	600	200	300	400	500	600
Urea	(60 Da)	191	246	272	285	291	196	282	344	388	418	199	293	376	445	502
Phosphate	(95 Da)	179	225	250	266	276	192	261	311	348	376	196	279	345	400	446
Creatinine	(113 Da)	184	232	258	273	282	194	269	323	362	391	198	285	357	416	465
Vitamin B12	(1.4 kDa)	148	178	199	214	226	164	207	239	264	285	174	227	267	301	329
Inulin	(5.2 kDa)	119	140	156	169	180	133	161	183	200	216	144	178	204	225	245
Cytochrome C	(12 kDa)	109	128	142	153	164	122	146	165	180	194	133	161	183	202	219
Myoglobin	(17 kDa)	93	108	119	129	138	104	123	137	150	161	114	135	152	166	180

Theranova 500

UF = 0 mL/min	Q_d = 300 mL/min					Q_d = 500 mL/min					Q_d = 800 mL/min				
Q_b (mL/min)	200	300	400	500	600	200	300	400	500	600	200	300	400	500	600
Urea	192	250	276	288	294	199	285	351	397	428	200	295	381	454	515
Phosphate	182	230	256	271	281	194	267	320	358	388	197	283	354	413	462
Creatinine	186	237	263	278	286	196	274	331	372	402	199	288	365	428	481
Vitamin B12	152	185	206	222	235	169	215	249	277	299	178	236	280	317	348
Inulin	124	147	164	178	189	139	170	193	213	230	150	188	216	241	262
Cytochrome C	114	134	150	162	173	128	155	175	192	208	139	171	196	217	235
Myoglobin	98	114	127	138	148	110	130	147	161	173	120	144	163	180	195

20 - Bench data – Clearance in vitro (mL/min)

UF = 10 mL/min	Q_b = 700 mL/min
Q_b (mL/min)	400
Chitinase-3-like protein 1 [YKL-40]	30

Typical values measured with Theranova 400 in human plasma (total protein conc. 55 g/L)
Measured according Boschetti-de-Fierro et al. Contrib Nephrol (2017) 191:100–114

21 - Clinical data (Theranova 400 dialyzer)

(1) PERCOM studies [NCT02377570, NCT02377622]
(Kirsch et al. Nephrol Dial Transplant (2017) 32: 165–172)

In two prospective, open-label, controlled, randomized crossover pilot studies, conducted in two dialysis centers in Germany and Austria, 39 prevalent HD patients were studied to compare middle and small molecule removal during single mid-week HD sessions using novel medium cut-off (MCO) membranes (including Theranova) with contemporary high-flux membranes during HD and HDF. The primary outcome was overall clearance of lambda free immunoglobulin light chains (λ FLC).
Secondary outcomes included overall clearances, pre-to-post reduction ratios of middle molecules and albumin removal into spent dialysate. MCO HD had increased removal of a wide range of middle molecules compared with high-flux HD, and exceeded the removal of high-volume HDF for large solutes, particularly YKL-40 and λ FLC, where HD with the MCO membranes achieved an increased reduction ratio versus the comparator.

	Mean Reduction Ratio (%)		Mean Overall Clearance (mL/min)	
Q_B/D_Q (mL/min)	300/500	400/600	300/500	400/600
β2-microglobulin [β2m] (12 kDa)	71.5	78.5	67.9	84.7
Myoglobin (17 kDa)	63.1	67.9	52.0	58.7
Kappa free light chains [κ-FLC] (23 kDa)	66.3	72.9	26.2	35.0
Complement Factor D [CFD] (24 kDa)	56.9	63.0	26.5	26.3
α1-microglobulin [α1m] (33 kDa)	21.7	24.8	3.8	3.3
Chitinase-3-like protein 1 [YKL-40] (40 kDa)	60.5	63.6	Only Reduction Ratio available	
Lambda free light chains [λ-FLC] (45 kDa)	42.5	48.1	8.5	10.0

	Albumin Removal (g/treatment)	
Q_B/D_Q (mL/min)	300/500	400/600
Median (range)	2.9 (1.5-3.9) g/treatment	3.2 (1.9-3.9) g/treatment

(2) Theranova 400 Randomized Controlled Trial [NCT03257410]

(Weiner et al. Efficacy and Safety of Expanded Hemodialysis with the Theranova 400 Dialyzer: A Randomized Controlled Trial. Clin J Am Soc Nephrol. 2020 Sep 7;15(9):1310-1319. doi: 10.2215/CJN.01210120. Epub 2020 Aug 25.)

A randomized controlled open-label trial was conducted in 21 centers in the US to evaluate the effectiveness and safety of expanded HD with the Theranova dialyzer. The objective of the study was to compare expanded HD with Theranova versus HD with Elisio-17H, a similar size high-flux dialyzer. The primary safety endpoint was the pre-dialysis serum albumin level after 24 weeks of treatment. The primary effectiveness endpoint was the reduction ratio of λ free light chains at 24 weeks of treatment. Secondary endpoints included reduction ratio of other middle to large molecules. 172 clinically stable maintenance hemodialysis patients were randomized to receive thrice weekly in-center dialysis with Theranova 400 or Elisio-17H over 24 weeks of treatment. Mean age was 59 ± 13 years, 39% were women, 40% Black/African American, and mean dialysis vintage was 5 ± 4 years. Of 86 patients randomized to each dialyzer, 65 completed the trial in each group. The study device-related AE incidence and AE incidence rate were comparable between the study device and control groups. There were no SAEs related to either device. The reduction ratio for the removal of λ free light chains was significantly higher in the Theranova group compared to the Elisio-17H group after 4 weeks and 24 weeks. Pre-dialysis serum albumin levels were similar between groups after 24 weeks, consistent with non-inferiority of the Theranova dialyzer in maintaining pre-dialysis serum albumin levels after 24 weeks of treatment. Among secondary endpoints, Theranova demonstrated superior removal of middle to large molecules as demonstrated by significantly larger reduction ratios at 4 and 24 weeks for complement factor D and κ free light chains (p<0.001). Theranova did not demonstrate statistically-significant removal of IL-6 as compared to the control and therefore additional statistical analysis of subsequent secondary endpoints (TNFα, β2-microglobulin and Kt/V urea) were not conducted due to the hierarchical methodology used for the assessment of secondary endpoints.

Mean ± STD Reduction Ratio (%)	Theranova 400	ELISIO 17H
Lambda free light chains [λ-FLC] (45 kDa)	33.3±11.0*	17.2±12.9
Complement Factor D [CFD] (24 kDa)	45.0±10.4*	23.6±12.1
Kappa free light chains [κ-FLC] (23 kDa)	63.8±11.8*	50.0±13.2
β2-microglobulin [β2m] (12 kDa)	73.6±10.4	65.4±9.4

Theranova 400: Weight 89.8±21.4 kg, time 3.72±0.48 h, Q_B 389±51 mL/min, Q_D 644±90 mL/min, UF 2.4±1.1 L
ELISIO 17H: Weight 96.5±27.7 kg, time 3.72±0.60 h, Q_B 396±57 mL/min, Q_D 639±93 mL/min, UF 2.6±1.1 L
Reduction ratios are corrected for the decrease in total extracellular volume due to fluid removal (hemoconcentration).
* Statistical significance (p<0.001)

At Week 24, there was a significant difference in the mean change from baseline of pre-dialysis levels of λ FLCs between the two groups (-19.40 mg/L [±31.635] in the Theranova group versus 1.75 mg/L [±29.946] in the control group; p=0.0002) as well as a difference in the pre-dialysis levels of κ FLCs (-84.81 mg/L [±97.358] in the Theranova group versus -43.01 mg/L [±75.677] in the control group; p=0.0012).

Pre-dialysis serum albumin levels (g/dL)

Group	Baseline	Week 4	Change vs Baseline Week 4	Week 8	Change vs Baseline Week 8	Week 24
Control	4.00±0.28	4.01±0.28	0.00±0.20	4.01±0.26	0.00±0.22	4.02±0.39
Theranova	4.04±0.31	3.97±0.31	-0.08±0.24 (-2%)	3.93±0.28	-0.11±0.25 (-3%)	4.03±0.28

Although there was a small, but statistically-significant reduction in serum albumin noted at Weeks 4 and 8, changes from baseline were not statistically significantly different between the two study groups at Week 12 and thereafter. The primary safety endpoint of this study was the pre-dialysis serum level of albumin after 24 weeks of treatment, which was not significantly different (two-sided 95% confidence interval: -0.098, 0.059) in the Theranova 400 group compared to the control group. The analysis of the endpoint confirmed that Theranova 400 is non-inferior to Elisio-17H in maintaining pre-dialysis serum albumin after 24 weeks of treatment based on a 5% non-inferiority margin (-0.1765 g/dL).

There was also no significant difference in the mean change from baseline for pre-dialysis levels of: Factor VII (50 kDa), Protein C (53-62 kDa) and Factor II (72 kDa) after 12 weeks and after 24 weeks of treatment; Vitamin A after 4 weeks and 24 weeks of treatment; and nPNA (normalized protein nitrogen appearance) after each 4 weeks of treatment.

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