DIASAFE® plus
Ultrapure Dialysate, Ultrasafe

Protecting the Endothelium

Fresenius Medical Care
Fluid quality is paramount

Ultrapure dialysate ensures fluid quality for successful dialysis

- Hemodialysis (HD) patients are typically exposed to > 360 liters of dialysate per week

- Bacterial endotoxins in contaminated dialysate can enter the blood compartment with undesirable consequences\(^1,2\)

- Endotoxin transfer from dialysate to blood compartment (backtransport) occurs by backdiffusion along a concentration gradient and by backfiltration or convection through a pressure gradient\(^1\)

**Low molecular weight fragments of bacterial endotoxins, small enough to pass across both low- and high-flux dialyser membranes (MW < 2000 Da), enter the bloodstream and activate leukocytes, resulting in chronic inflammation and poor patient outcomes**

- Whether you’re using high-flux or low-flux dialysis, the risk of endotoxin transfer can be managed by ensuring dialysate quality is optimized\(^1\)
Endotoxin contamination leads to poor patient outcomes

Undesirable consequences of poor fluid quality

- Endotoxin accumulation leads to monocyte activation, pro-inflammatory cytokine production and, ultimately, chronic inflammation.  

![Diagram with Endotoxins leading to Chronic Inflammation, including:
- Atherosclerotic CVD risk increased
- Lowered EPC response
- AGE & β₂M plasma accumulation
- Residual function lost
- Malnutrition & anorexia
- Poor patient outcomes & wellbeing: Headache, Myalgia, Exhaustion, Hypotension, Fever
- Increased morbidity and mortality

CVD = cardiovascular disease; AGE = advanced glycation end-products; β₂M = β₂-Microglobulin
Inflammation & endothelial injury cause CVD in ESRD patients

- CVD is the main cause of morbidity and mortality in ESRD patients.

- In addition to traditional risk factors, causes of progressive atherosclerotic CVD in ESRD patients include:
  - **Chronic inflammation** – shown by elevation of inflammatory markers such as CRP and IL-6
  - Chronic inflammation also leads to malnutrition
  - **Endothelial injury and dysfunction** – manifest as impaired nitric oxide-mediated vasoresponsiveness in hemodialysis patients

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**Diagram:**

- **Lipopolysaccharide (LPS)**
  - Activation of the complement system
  - Activation of immune cells
  - Release of pro-inflammatory cytokines: IL-1, IL-6 (↑ CRP), IL-8, TNF-α
  - Production of lipid-mediators: prostaglandins, thromboxanes, platelet activating factor
  - Release of reactive oxygen species (ROS)
  - **Endothelial injury**

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**Abbreviations:**
- CRP = C-reactive protein; IL-6 = interleukin-6;
- ESRD = end-stage renal disease; TNF-α = tumor necrosis factor-α
- LPS = endotoxin fragments
Ultrapure dialysate significantly reduces inflammation

• Ultrapure dialysate prepared using DIASAFE® plus significantly reduced CRP and interleukin-6 (IL-6) in HD patients, compared to baseline and the conventional dialysate group, in a 12-month study (n = 30). *

![Graph showing CRP levels over time for conventional and ultrapure dialysates.](image)

• In a similar study, at study end (12 months), in the ultrapure dialysate group: *
  - 46% (11/24) had CRP levels below the expected normal value
  - 50% (12/24) had IL-6 concentrations within the normal range
  - Patients had improved nutritional status
DIASAFE® plus – the critical step towards best practice

Best Practice Guidelines recommend using ultrapure dialysate to improve patient outcomes

- Regular and effective disinfection procedures are integral to hygienic maintenance of the water treatment system – follow European Best Practice Guidelines (EBPG)\textsuperscript{11}
- Use dialysis membranes with high endotoxin retention capacity.
- Make ultrapure dialysate fluid mandatory in your facility, i.e.: use DIASAFE® plus

<table>
<thead>
<tr>
<th>Recommended Microbiological Quality Standards</th>
<th>Microbial contamination (CFU/ml)</th>
<th>Bacterial endotoxins (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US standard (AAMI)</td>
<td>&lt; 200</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>European standard (ERA-EDTA)</td>
<td>&lt; 100</td>
<td>&lt; 0.25</td>
</tr>
<tr>
<td>ULTRAPURE</td>
<td>&lt; 0.1</td>
<td>&lt; 0.03</td>
</tr>
</tbody>
</table>

What are the cost implications?

- **DIASAFE® plus** filters cost only a fraction of total treatment cost
- **DIASAFE® plus** is cost-effective due to its long functional life (100 treatments/12 weeks)
- **DIASAFE® plus** acquisition costs are offset by cost savings e.g. due to reduced recombinant human erythropoietin (rHuEPO) dose requirement\textsuperscript{8}
- **DIASAFE® plus** provides significant clinical benefits that may reduce long-term costs:
  - Reduced cardiovascular morbidity\textsuperscript{9}
  - Improved nutritional status\textsuperscript{10}
  - Increased seroconversion after hepatitis B vaccination\textsuperscript{12}
DIASA® plus ensures ultrapure dialysate

**DIASA® plus** – a key component of your dialysis system is located at the end of the water treatment pathway to ensure delivery of ultrapure dialysate.

- Endothelial injury resulting from oxidative processes and inflammation is central to accelerated atherosclerosis seen in ESRD.
- High endotoxin retention capacity of the Fresenius Polysulfone membrane prevents transfer of microbial contaminants – producing ultrapure dialysate.

**DIASA® plus reduces the bacterial concentration of dialysate**

- In standard HD, **DIASA® plus**:
  - Reduces endotoxin concentration by 99.5%.
  - Functions optimally for up to 12 weeks.

**DIASA® plus reduces the endotoxin concentration of dialysate**
DIASAFE® plus...
for better patient outcomes

Reduces risk of progressive atherosclerotic CVD:

- Cardiovascular disease remains the leading cause of death for dialysis patients.
- Ultrapure dialysate significantly reduces inflammation.
- Reduction of micro-inflammation with ultrapure dialysate reduced the rate of cardiovascular events in a 3-year study (n = 60).

![Ultrapure dialysate fluid prepared using DIASAFE® plus reduces the risk of a cardiovascular event](chart)

<table>
<thead>
<tr>
<th>CRP &gt; 0.5 mg/dl</th>
<th>CRP &lt; 0.5 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dialysate</td>
<td>11</td>
</tr>
<tr>
<td>Ultrapure dialysate</td>
<td>0</td>
</tr>
</tbody>
</table>

Reduces risk of dialysis-related amyloidosis, and bone & joint disorders:

- β₂-Microglobulin (β₂M) and its advanced glycation (AGE) modified form, stimulate cytokine secretion in bone and joints, leading to:
  - Dialysis-related amyloidosis
  - Increased risk of joint and bone disorders, such as carpal tunnel syndrome
- Ultrapure dialysate treatment significantly decreased plasma levels of β₂M and pentosidine compared with conventional dialysate treatment.

![Ultrapure dialysate reduces plasma levels of β₂M](chart)

<table>
<thead>
<tr>
<th>β₂-Microglobulin (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional dialysate</td>
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<tr>
<td>Ultrapure dialysate (1 month)</td>
</tr>
<tr>
<td>Ultrapure dialysate (6 months)</td>
</tr>
</tbody>
</table>

*P < 0.05 versus conventional dialysate at baseline
DIASAFE® plus...
for better patient outcomes

Reduces total treatment cost due to improved rHuEPO response:

- HD patients switched to ultrapure dialysate (from conventional dialysate) had improved responsiveness to rHuEPO\(^4\)

- Average sustained reduction in rHuEPO of 33% in this study translates to a potential saving of 1,900 units/week of rHuEPO\(^6\)

**Ultrapure dialysate fluid prepared using DIASAFE® plus reduces the dose requirement for recombinant erythropoietin (rHuEPO)**\(^6\)

Reduces risk of malnutrition:

- Ultrapure dialysis resulted in improved nutritional status in HD patients, measured by:\(^6\)
  - Increased body weight
  - Increased mid-arm muscle circumference
  - Increased serum albumin concentration
  - Increased humoral factor levels

**Ultrapure dialysate prepared using DIASAFE® plus improves nutritional status: change from baseline in dry weight**\(^8\)
**DIASAFE® plus...**

for better patient outcomes

Reduces rate of decline of residual function

- Residual renal function declines with time on dialysis therapy
- Ultrapure dialysate treatment slowed down the loss of residual function, compared with conventional dialysate treatment in a 2-year study (n = 30)²

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**Ultrapure dialysate prepared using DIASAFE® plus preserves residual renal function: residual creatinine clearance**

- Conventional dialysate
- Ultrapure dialysate

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**Ultrapure dialysate prepared DIASAFE® plus preserves residual renal function: daily urine volume**

- Conventional dialysate
- Ultrapure dialysate
DIASAFE® plus...
for better patient outcomes

Reduces plasma levels of advanced glycation end products (AGE)

- Increased oxidative stress and impaired AGE removal by the damaged kidney contribute to AGE accumulation, resulting in inflammation, endothelial injury and eventually CVD\(^\text{10}\).

[Graph showing the effect of DIASAFE® plus on AGE accumulation]

- Ultrapure dialysate treatment reduced AGE accumulation compared with conventional dialysate treatment in long-term hemodialysis patients \((n = 71)\)^{15}.

Improves response to hepatitis B vaccine

- Hepatitis B virus infection remains a serious threat to hemodialysis patients despite improvements in infection control and dialysis techniques\(^\text{32}\).

- Ultrapure dialysate treatment improved response rate to hepatitis B vaccination compared with conventional dialysate treatment in early hemodialysis patients \((n = 72)\)^{12}.

[Graph showing the effect of DIASAFE® plus on hepatitis B antibody titer]
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Ultrapure dialysate significantly reduces inflammation
**DIASAFE® plus** – the critical step towards best practice
**DIASAFE® plus** ensures ultrapure dialysate
**DIASAFE® plus... for better patient outcomes**
  - Reduces risk of progressive atherosclerotic CVD
  - Reduces risk of dialysis-related amyloidosis, and bone & joint disorders
  - Reduces total treatment cost due to improved rHuEPO response
  - Reduces risk of malnutrition
  - Reduces rate of decline of residual function
  - Reduces plasma levels of advanced glycation end products (AGE)
  - Improves response to hepatitis B vaccine

References