Baxter

Extraneal

(ICODEXTRIN 7.5%)

SOLUTION FOR PERITONEAL DIALYSIS

START WITH EXTRANEAL SOLUTION

ONE DAILY BAG. MULTIPLE BENEFITS.

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WHAT IS **EXTRANEAL** (ICODEXTRIN 7.5%) SOLUTION FOR PERITONEAL DIALYSIS?

EXTRANEAL solution is a non-glucose, Icodextrin solution for the long dwell, prescribed by nephrologists for 20+ years.

START WITH **EXTRANEAL** SOLUTION

In comparison to glucose-based solutions, prescribing one bag a day, from the start of PD therapy, can reduce glucose exposure over time[1-7] and may positively impact fluid management.[3, 8-16] These benefits may increase time on PD therapy[2, 15-20] and improve patient survival.[4-8, 21-25]

Icodextrin's clinical benefits are endorsed by multi-disciplinary organisations such as the International Society for Peritoneal Dialysis (ISPD).[15]

Prescribing one bag of **EXTRANEAL** solution from the start of PD therapy may bring the following benefits to patient outcomes:

REDUCE GLUCOSE-RELATED RISK [1-7, 9, 29-32]

ACHIEVE FLUID BALANCE [3, 8-16, 33]

EXTEND TIME ON PD THERAPY [2, 15-20]

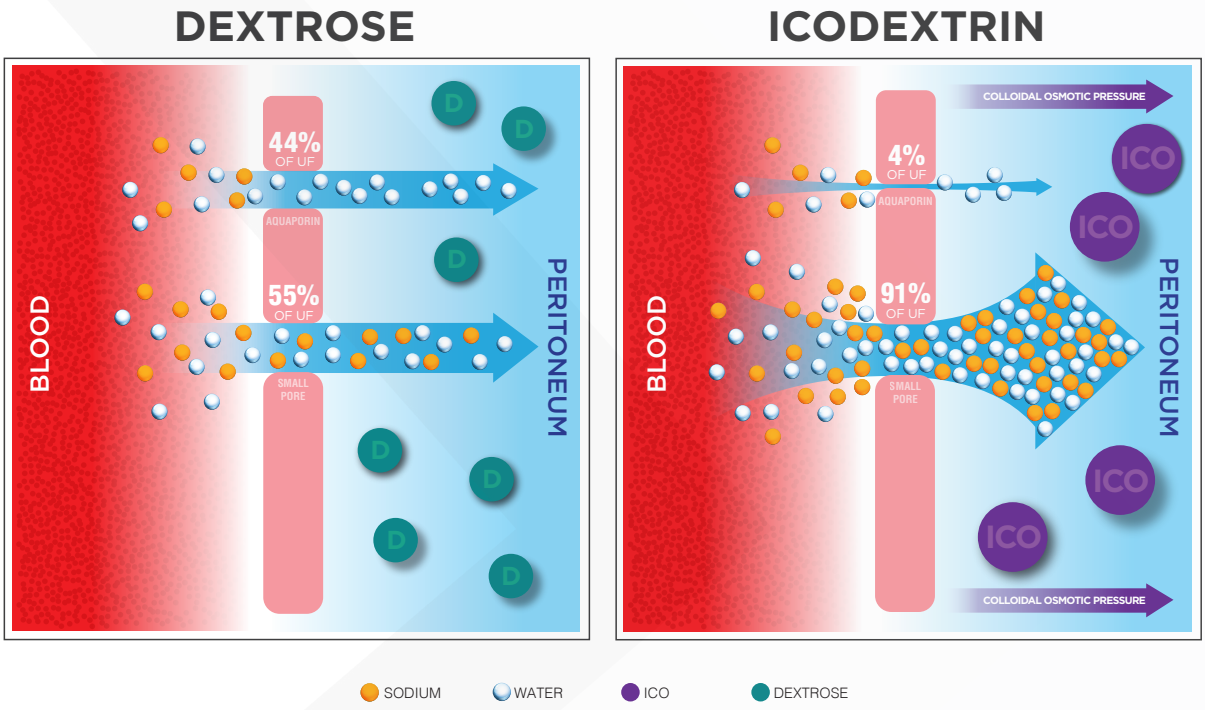
MAY IMPROVE SURVIVAL RATES [4-8, 17, 21-25, 34-36]

HOW DOES **EXTRANEAL** (ICODEXTRIN 7.5%) SOLUTION FOR PERITONEAL DIALYSIS WORK?

THE LONG DWELL

The dwell time is the prescribed period of time the dialysis fluid stays in the patient's abdomen. A short dwell is typically below four to six hours, while the long dwell is up to 16 hours.

The challenge over the long dwell is that glucose will be absorbed over time leading to gradual fluid resorption from the peritoneal cavity.



Devuyst, Oliver, and Bengt Rippe. "Water transport across the peritoneal membrane." *Kidney International*, 2014: 750-758.

ICODEXTRIN VS. 2.5% GLUCOSE-BASED SOLUTIONS

Icodextrin contains large molecules that generate a colloidal osmotic pressure.[26] Icodextrin is isosmotic to plasma and, unlike dextrose-based solutions, does not generate a significant aquaporin-mediated water-only ultrafiltration.[26, 27] Icodextrin generates ultrafiltration predominantly through the peritoneal small and large pores – not aquaporins – which induces sustained ultrafiltration over the whole long dwell and more sodium removal compared to 2.5% dextrose.[14, 26]

ENDORSED BY GUIDELINES

The International Society for Peritoneal Dialysis (ISPD) recommends the use of Icodextrin solution, such as **EXTRANEAL** (Icodextrin 7.5%) solution for peritoneal dialysis.[15]

1. **Compared with glucose, use of Icodextrin solution can translate into improved fluid status and fewer episodes of fluid overload[15] (Grade 1A).[a]**

2. **ISPD guidelines state that using Icodextrin solution and automated peritoneal dialysis (APD) may mitigate the mortality risk associated with high membrane transporters (practice point).[15]**

EXTRANEAL SOLUTION IS WIDELY STUDIED. THE FOLLOWING RANDOMISED TRIALS INVOLVE EXTRANEAL (ICODEXTRIN) SOLUTION

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Takatori Y, Akagi S, Sugiyama H, et al. Icodextrin increases technique survival rate in peritoneal dialysis patients with diabetic nephropathy by improving body fluid management: a randomized controlled trial. Clin J Am Soc Nephrol. 2011;6:1337-1344.

Wolfson M, Piraino B, Hamburger RJ, Morton AR. A randomized controlled trial to evaluate the efficacy and safety of Icodextrin in peritoneal dialysis. Am J Kidney Dis. 2002;40:1055-1065.

a. Statement graded by ISPD as Grade 1A (strength of recommendation = "We recommend"; certainty of supporting evidence = "high certainty).

THE BENEFITS
REDUCE GLUCOSE-RELATED RISK

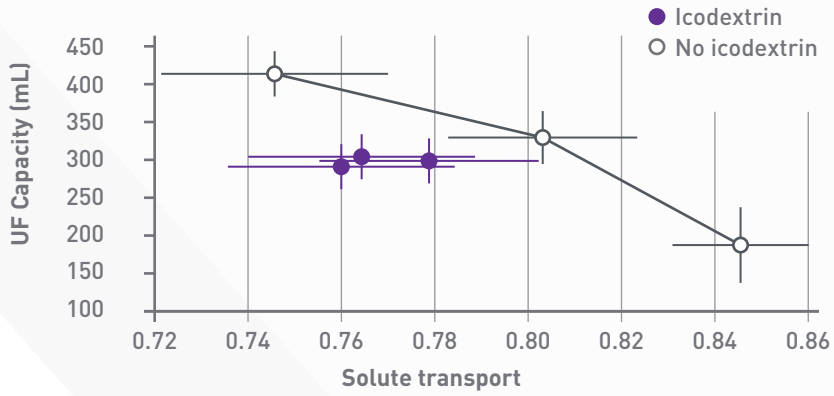
GLUCOSE EXPOSURE

EXTRANEAL solution is a (non-glucose) Icodextrin solution.[28] Prescribing PD patients with Icodextrin solution, such as **EXTRANEAL** (Icodextrin 7.5%) solution from the start, limits glucose exposure during PD therapy over time, minimising changes to the peritoneal membrane.[1-7]

WHY IS IT IMPORTANT?

Long-term glucose exposure contributes to both structural and functional changes to the peritoneal membrane over time, which may result in a transfer to HD therapy.[1-7]

LONGITUDINAL MEMBRANE FUNCTION ACCORDING TO BASELINE USE OF ICODEXTRIN OR NO ICODEXTRIN SOLUTION*



* The data points represent paired mean values (±SE) for patients remaining throughout the study that move from left to right at baseline, 12 and 24 months.
Figure adapted from **Davies SJ, et al.** Kidney Int. 2005; 67:1609–1615.spo

ICODEXTRIN SOLUTION FOR THE LONG DWELL EXCHANGE HELPS MAINTAIN STABLE PERITONEAL MEMBRANE FUNCTION COMPARED WITH GLUCOSE SOLUTIONS[1]

Peritoneal glucose exposure is associated with alterations in peritoneal membrane structure[29, 30] and function[31, 32] that can lead to fluid overload.

A longitudinal, prospective membrane function analysis of functionally anuric patients treated with peritoneal dialysis solutions (n=177). Patients receiving Icodextrin solution (n=82) had no change in ultrafiltration capacity and a small but insignificant change in solute transport over 24 months.[9]

Patients not receiving Icodextrin solution (n=95) experienced a significant decline in ultrafiltration capacity and an increase in solute transport.[9]

ULTRAFILTRATION & FLUID BALANCE

Icodextrin solution, such as **EXTRANEAL** (Icodextrin 7.5%) solution may improve clinical outcomes by increasing ultrafiltration and maintaining fluid balance.[3, 8-16]

WHY IS IT IMPORTANT?

Achieving fluid balance throughout the time on PD therapy is critical in the success of therapy. Fluid imbalance may result in patient weight gain, swelling of legs and breathlessness and ultimately may result in transfer to HD and increased risk of mortality.[3, 8-16, 33]

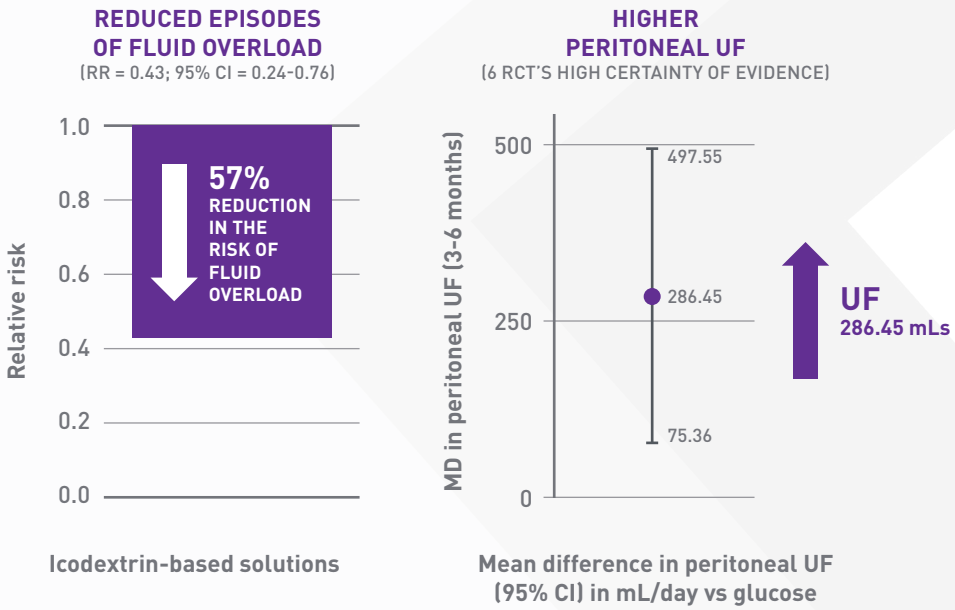


Figure adapted from **Goossen K, et al.** Am J Kidney Dis. 2020;75(6):830-846

ICODEXTRIN SOLUTION FOR THE LONG DWELL EXCHANGE INCREASES ULTRAFILTRATION VOLUME AND IMPROVES FLUID STATUS COMPARED WITH GLUCOSE SOLUTIONS[8-13]

- In a meta-analysis of patients who received PD during randomised clinical trials (RCTs) conducted between 1994 and 2018, use of Icodextrin solutions was associated with greater mean net long-dwell ultrafiltration vs. glucose after ≤6 weeks (mean difference = 282.49 mL; RCTs = 6; n = 694; high certainty), 3–6 months (mean difference = 286.45 mL; RCTs = 6; n = 362; high certainty), and 1–2 years of treatment (mean difference = 237.38 mL; RCTs = 3; n = 104; low certainty).[8]
- In the same meta-analysis, use of Icodextrin solutions was associated with fewer episodes of uncontrolled fluid overload vs. glucose solutions (risk ratio [RR] = 0.43; 95% confidence interval [CI] = 0.24–0.76).[8]
- RCTs showed that Icodextrin solutions, such as **EXTRANEAL** solution, reduced extracellular fluid volume compared with 2.27% glucose solution in high or high–average transporters treated with continuous ambulatory peritoneal dialysis (CAPD)[9] or CAPD/APD[10] and compared with 1.36% glucose solution in PD patients.[11]
- A systematic review of RCTs found that the use of Icodextrin solutions, such as **EXTRANEAL** solution, for the long dwell combined with appropriate management of the short dwells (adjustment of glucose concentration) reduces the number of episodes of uncontrolled fluid overload.[12]
- Improved fluid control was exhibited following treatment with Icodextrin solution vs. glucose solution in a prospective, open-label RCT of 53 CAPD patients with acute peritonitis (0% of patients required additional hypertonic PD exchanges for fluid control in the Icodextrin treatment group vs. 35.5% of patients in the control group; P = 0.001).[13]

THE BENEFITS
EXTEND TIME ON PD THERAPY

PATIENT TIME ON THERAPY

When prescribed from the onset of PD, one daily bag of Icodextrin solution, such as **EXTRANEAL** (Icodextrin 7.5%) solution for the long dwell may increase patient time on therapy.[2, 15-20]

WHY IS IT IMPORTANT?

Extended time on therapy supports key priorities for end-stage kidney disease (ESKD) patients and clinicians, including staying on the modality of patients' choice, preserving residual kidney function (RKF) and remaining active in society.[2, 15-20]

THE ECONOMIC IMPACT OF EXTENDING TIME ON PD THERAPY VS. IN-CENTER HD BASED ON THE ESTIMATED COST SAVINGS IN AUSTRALIA

1.21 YEARS INCREASED MEAN TIME ON PD[2, 18]

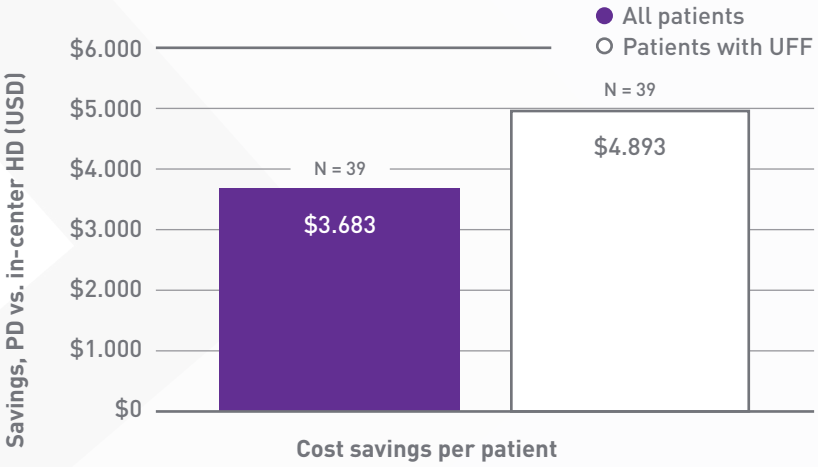


Figure adapted from **Johnson DW, et al.** Adv Perit Dial. 2003;19:81-85.

Australian prospective open label study

Patients who were considered to be at the point of transfer from PD to haemodialysis (HD) due to refractory fluid overload.

EXTRANEAL SOLUTION (ICODEXTRIN) MAY EXTEND TIME ON PD THERAPY FOR SOME PATIENTS,[2,18] WITH POTENTIAL COST SAVINGS.[2]

- In an Australian prospective open-label study of patients who were considered to be at the point of transfer from PD to haemodialysis (HD) due to refractory fluid overload, changing just one PD exchange with 4.25% glucose solution to **EXTRANEAL** solution was shown to increase time on PD by a mean of 1.21 years (95% CI = 0.80–1.62 years).[2]
- Using a computer model, the economic impact of extending time on PD therapy was approximately US$3,700 per patient per year (approximately US$4,900 in patients with ultrafiltration failure) vs. in-centre HD (savings converted from AU$ to US$ in approx. 2002), based on savings for direct therapy costs, calculated using retrospective data from the 1998 Cairns costing study in Queensland, Australia.[2]
- Use of **EXTRANEAL** solution was shown to increase technique survival rate in diabetic nephropathy patients vs. the use of 1.5% or 2.5% glucose solution alone (technique survival rate after 24 months: 71.4% vs. 45.0%; P = 0.0365) in a prospective multicenter RCT of 41 PD patients.[18]

SURVIVAL RATES

Icodextrin solution, such as **EXTRANEAL** (Icodextrin 7.5%) solution may increase patient survival rates through cardiovascular risk reduction and better fluid balance.[4-8, 21-25] Patient survival is a primary concern for clinicians and PD patients, as presented in the SONG-PD recommendations.[17]

WHY IS IT IMPORTANT?

Cardiovascular events alone account for about 40-60% of PD patient deaths,[17] often potentially related to metabolic changes. Therefore, seeking a non-glucose solution may reduce the risk of cardiovascular-related deaths.[25]

EXTRANEAL SOLUTION AND OTHER ICODEXTRIN SOLUTIONS ASSOCIATED WITH A REDUCED MORTALITY RISK[8]

THE ODDS RATIO OF MORTALITY 0.49 (0.24, 1.00)

META-ANALYSIS
19 RCTs

1994 and 2018

n = 1,685

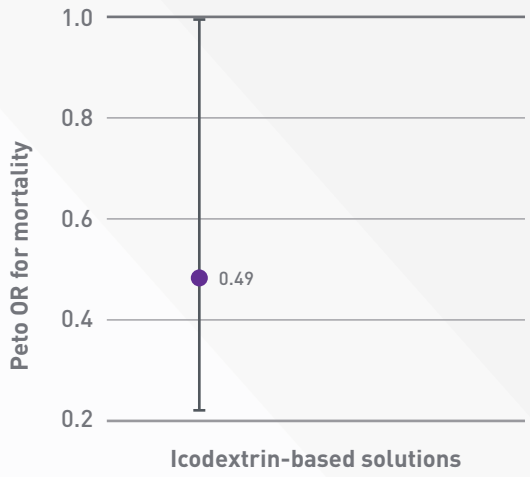


Figure adapted from **Goossen, et al.** Am J Kidney Dis. 2020;75(6):830-846

EXTRANEAL SOLUTION (ICODEXTRIN) MAY BE ASSOCIATED WITH IMPROVED PATIENT SURVIVAL.[8, 34-36]

- In a meta-analysis of 1,685 patients who received PD during 19 RCTs conducted between 1994 and 2018, use of **EXTRANEAL** solution and other Icodextrin solutions was associated with a decreased mortality risk compared with glucose solutions (Peto odds ratio [OR] = 0.49; 95% CI = 0.24–1.00).[8]
- In a retrospective analysis of 2,163 patients from 54 centres in Korea who initiated PD from July 2003 to December 2006, death occurred in 92 (14.4%) patients in the **EXTRANEAL** solution group (patients who used **EXTRANEAL** solution for >50% of PD duration) vs. 128 (20.0%) in the non-Icodextrin group (hazard ratio [HR] = 0.69; 95% CI = 0.53–0.90; P = 0.006).[34]
- Reanalysis of the same data using a different and more rigorous analytic method (Icodextrin as a time-dependent covariate)[36] found that **EXTRANEAL** solution was associated with a 40% reduction in the risk of death (HR = 0.60; 95% CI = 0.47–0.76; P < 0.001).[35]
- In a retrospective analysis of 4,914 patient records obtained from a Taiwanese insurance database over a 5-year period, the risk of death was 26% lower in Icodextrin users receiving PD compared with non-users receiving PD (HR = 0.74; 95% CI = 0.63–0.86).[36]

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