Instructions for Running the PD ADEQUEST® 2.0 Extraneal Patch

Please print this document to use as a reference during the installation of this Extraneal Patch.

On the PD Adequest site of www.baxter.com - click on Download PD Adequest Extraneal Patch Now

File Download
- Click on Run this program from its current location

Click on ![OK](image)

If you receive a Security Warning prompt, click on Yes

You are now ready to begin the process of updating PD Adequest to include Extraneal.
You will be prompted with the current settings in PD ADEQUEST® 2.0:

The settings that were selected at the installation of PD ADEQUEST will be displayed; the only setting that needs to be changed is the Available Solution option.

Click on

There should be a check mark displayed in the box next to Include Extraneal, if not, click on the box indicating to Include Extraneal, the box will then display a check mark.  Do not change any other settings.

Click on

Click on

Click on
To verify if the Extraneal Patch was successfully installed, Click on the PD Adequest Icon, Select a patient, click on Regimen, CAPD, under the Percent Dextrose column there is a drop down list with available solutions, it will now include Extraneal as an available solution.

Extraneal Modeling in PD ADEQUEST 2.0

Introduction
This letter provides the user with information regarding how PD ADEQUEST 2.0 currently models ultrafiltration and glucose absorption for long-dwell exchanges done with Extraneal as well as information regarding potential future enhancements to this modeling.

Background
Extraneal is a peritoneal dialysis (PD) solution containing 7.5 grams of icodextrin per deciliter of solution. Icodextrin is a polydispersed glucose polymer preparation consisting of glucose polymers (or dextrins) ranging in size from 2 to 1000 carbohydrate units (expressed in terms of degrees of polymerization). This polydispersed glucose polymer serves as the osmotic agent governing ultrafiltration during a single exchange with Extraneal. Due to the large molecular weight (MW) distribution of the dextrins, fluid removal with Extraneal is achieved primarily by the exertion of an "oncotic" or colloid osmotic pressure gradient as opposed to the crystalloid osmotic pressure gradient achieved with glucose containing solutions (e.g., Dianead 1.5%, 2.5% or 4.25% dextrose).

EXTRANEAL is indicated for a single daily exchange for the long (8 to 16 hour) dwell during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of chronic renal failure. EXTRANEAL is contraindicated in patients with a known allergy to cornstarch or icodextrin or in patients with glycogen storage disease. In clinical trials the most frequently reported adverse events occurring in ≥ 10% of patients, and more common in EXTRANEAL patients than in control patients, were peritonitis (26% vs 25%), upper respiratory infection (15% vs 13%), hypertension (13% vs 8%), and rash (10% vs 5%). These were also observed in control patients. The most common treatment-related adverse event for EXTRANEAL patients was skin rash (5.5% vs 1.7%). Since falsely elevated glucose levels have been observed with blood glucose monitoring devices and test strips that use glucose dehydrogenase pyrroloquinolinequinone (GDH PQQ)–based methods, GDH PQQ-based methods should not be used to measure glucose levels in patients administered EXTRANEAL. The manufacturer(s) of the monitor and test strips should be contacted to determine if icodextrin or maltose causes interference or falsely elevated glucose results. Patients with insulin-dependent diabetes may require modifications of insulin dosage following initiation of treatment.

Modeling Assumptions
The MW distribution of dextrins, as measured by size exclusion chromatography, has been established and summarized for five (5) representative glucose polymer size classes (or subfractions) of the polydispersed solution. The five subfractions correspond to distinct ranges of carbohydrate units. The number of carbohydrate units is represented by the degree of polymerization (DP). Based on a log-normal distribution, the average MW and osmolarity can be determined for each subfraction resulting in five (5) "average" dextrins. PD ADEQUEST 2.0 models ultrafiltration assuming the entire solution can be adequately characterized by these five (5) "average" dextrins. Specifically, PD ADEQUEST 2.0 computes the necessary three-pore model parameters (e.g., mass transfer area coefficients, reflection coefficients, etc.) for each of these five "average" dextrins. It then models net ultrafiltration and glucose absorption using these parameters in combination with default starting blood concentrations. Davies1 reports an average baseline blood concentration for maltose (DP =2) of 0.04 mg/mL (or 0.12 mmol/L) for 91 patients. In the absence of either average values or patient-specific values for the blood levels of the five "average" dextrins, PD ADEQUEST 2.0 uses default baseline blood levels that are less than or equal to the average baseline maltose value reported by Davies. Table 1 below shows the specific composition of the five "average" dextrins as modeled in PD ADEQUEST 2.0.
Glucose Absorption
PD ADEQUEST models glucose absorption (grams) based solely on the presence of glucose in the dialysate and blood. Consequently, for a single exchange done using Extranal, PD ADEQUEST 2.0 will predict negative glucose absorption since glucose is transported from the blood to the dialysate side in the absence of glucose in the infused Extranal solution. Although there is no direct glucose absorbed with the use of Extranal, there is total carbohydrate absorption caused by transporting higher degree glucose polymers across to the blood. PD ADEQUEST does not model total carbohydrate absorption; it only models that fraction of total carbohydrate absorption directly attributed to glucose absorption (see Figure 1).

Clinical Validation
An initial validation of how well the model and assumptions perform with respect to measured ultrafiltration was carried out using data from several published sources2-4, and results of the entire validation are currently being drafted for publication. The results from one study3 conducted by Douma et al (Kidney Int 53:1014-1021, 1998) are briefly summarized here. This study provides detailed kinetic results of an 8-hour dwell among ten (10) patients receiving a 7.5% icodextrin solution. Net ultrafiltration was measured via dilution of the volume marker, dextran 70, with sample values obtained at 10, 20, 30, 60, 120, 180, 240, 300, 360, 420, and 480 minutes post-infusion3. Modeled values were obtained from PD ADEQUEST 2.0 using mass transfer area coefficients estimated from 10, 120 and 240 minute data as well as other data that would normally be collected from a peritoneal equilibration test (PET). Figure 2 compares measured and modeled ultrafiltration using a concordance correlation coefficient described by Vonesh et al5. Overall, there was excellent agreement between measured and modeled values with an overall concordance correlation of 0.9856.

Summary and Future Directions
PD ADEQUEST 2.0 uses an approach similar to that described by Rippe and Levin6 for the modeling of icodextrin and the modeled values achieved with PD ADEQUEST closely mirror their simulated ultrafiltration profiles. However, as noted by Rippe and Levin6, and Amici et al7, one should expect an initial ultrafiltration that will be higher among patients when they first start using Extranal as compared to when they have been on Extranal for a period of time (typically within 1 to 2 weeks). This is because at initiation, patient blood levels of icodextrin (e.g., maltose, maltotriose) will be particularly low but after a 1-2 week period, these blood levels will reach a higher steady-state resulting in a lower osmotic gradient and consequently lower ultrafiltration. As the current version of PD ADEQUEST uses a set of default baseline blood levels of icodextrin, it is likely that modeled values will overpredict ultrafiltration for patients who are new to Extranal. Currently, work is being completed for the next release of PD ADEQUEST that will incorporate default steady-state blood levels of icodextrin that will better reflect patients who have been on Extranal for a period of time. These new default steady-state blood levels will reflect patient size and other characteristics and are aimed at being as patient-specific as possible without actually requiring icodextrin blood levels to be measured.

References
Table 1: Composition of Extraneal in terms of five "average" dextrins theoretically modeled within each class or subfraction of glucose polymers.

<table>
<thead>
<tr>
<th>Degree of Polymerization (DP)</th>
<th>MW Upper Bound (Daltons)</th>
<th>% Mass</th>
<th>Number Mean MW (Daltons)</th>
<th>Mass Mean MW (Daltons)</th>
<th>Average Osmolarity (mOsm/L)</th>
<th>Baseline Conc. (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10</td>
<td>1,639</td>
<td>5%</td>
<td>1,166</td>
<td>1,272</td>
<td>3.214*</td>
<td>0.12</td>
</tr>
<tr>
<td>11-31</td>
<td>5,044</td>
<td>21%</td>
<td>3,118</td>
<td>3,412</td>
<td>5.05092</td>
<td>0.12</td>
</tr>
<tr>
<td>32-123</td>
<td>19,961</td>
<td>48%</td>
<td>9,414</td>
<td>10,878</td>
<td>3.82428</td>
<td>0.12</td>
</tr>
<tr>
<td>124-277</td>
<td>44,931</td>
<td>20%</td>
<td>27,466</td>
<td>28,886</td>
<td>0.54612</td>
<td>0.12</td>
</tr>
<tr>
<td>278-1000</td>
<td>162,158</td>
<td>6%</td>
<td>56,702</td>
<td>59,549</td>
<td>0.07923</td>
<td>0.012</td>
</tr>
</tbody>
</table>

* 0.0042 mOsm/L computed for glucose (DP=1).
Figure 1. Carbohydrate absorption based on an initial 7.5% Extraneal exchange

Carbohydrate absorption based on an initial 7.5% Extraneal Exchange
Note: Total carbohydrate absorption reflects negative glucose absorption (shown as solid line). Total carbohydrate absorption at 8 and 12 hours (shown as dashed line) are from Davies (Perit. Dial Int. 14(S2):S45-S50, 1994)
Figure 2. Measured and modeled net ultrafiltration profile of 10 stable patients new to icodextrin. Measured (actual) values are those reported by Douma et al (Kidney Int 53:1014-1021, 1998) while modeled values are those obtained from PD ADEQUEST 2.0 in conjunction with kinetic parameters estimated from a modified PET (Douma, et al) and assuming default baseline icodextrin plasma levels as shown in Table 1. The concordance correlation of 0.9856 measures the level of agreement between measured and modeled ultrafiltration across all patients.

**Net Ultrafiltration Profile (mL)**

Solid line = Modeled Values, Points = Actual Data (Mean ± 2 SE)

Data Source:
Douma et al, Kid Int 1998; 53:1014-21