



MINISTRY for ENERGY and HEALTH  
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**DH CIRCULAR No. 278/2014**  
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**Attention All:** Consultants  
Medical Officers  
Pharmacists  
Pharmacy Technicians  
Nurses

**RE: Mannitol 15% Intravenous Infusion**

Please be informed that Mannitol Intravenous Infusion is currently available in a concentration of 15% instead of 20%.

The availability of mannitol 15% Intravenous Infusion follows the notification from Baxter that mannitol 15% intravenous solution (Baxter) will replace mannitol 20% intravenous solution (Baxter). More information is available in Annex 1.

Due to the difference in osmolarity between both solutions, slightly more volume of the 15% solution needs to be administered to obtain the same osmotic and diuretic effect. The dosage depends on the age, weight, clinical and biological condition of the patient and concomitant therapy. More information on the dosage regimen of the 15% solution is available on the summary of product characteristics via the following link:

<http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1390535259739.pdf>

For your attention please.

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**Informative document to be distributed to the countries in case of questions about the conversion from Mannitol 20% to Mannitol 15%****Rational**

Mannitol 20% is a supersaturated solution and potential precipitation of mannitol crystals is therefore possible. If this occurs, redissolution of crystals by slow warming is required before administration. For this reason Baxter decided to replace systematically our current Mannitol 20% products by Mannitol 15%.

Mannitol 15% is below the saturation concentration and hence using a Mannitol 15% concentration would minimize the risk of crystallization and related issue of re-dissolution practice.

As there is a difference in osmolarity between both solutions, the medical implication is the need to administer slightly more volume of a 15% solution versus 20% solution to obtain the same osmotic and diuretic effects. This needs to be considered in case of patients with fluid restriction.

**Physico-chemical background and evidence**

Both solutions, Mannitol 15% and Mannitol 20%, contain Mannitol dissolved in water, but Mannitol is sparingly soluble in water; this limited solubility regulates the crystallization of dissolved Mannitol in alignment with temperature changes.

The solubility of Mannitol in water is defined as the maximum amount of the Mannitol that will dissolve in pure water at a specified temperature; above this concentration, two phases will exist: a saturated aqueous solution and a solid phase.

| Temperature (°C) | Grams of Mannitol per 100 gram H <sub>2</sub> O | Temperature (°C) | Grams of Mannitol per 100 gram H <sub>2</sub> O |
|------------------|---|------------------|---|
| 0.0              | 10.4  | 40.0             | 34.6  |
| 5.0              | 11.9  | 60.0             | 47.6  |
| 10.0             | 13.7  | 50.0             | 64.4  |
| 15.0             | 16.0  | 70.0             | 86.2  |
| 20.0             | 18.6  | 80.0             | 115.0   |
| 25.0             | 21.6  | 90.0             | 150.0   |
| 30.0             | 25.2  | 100.0            | 197.0   |

Solubility of Mannitol in Water as function of the temperature (Seidell; Yi, Hatzivramidis, and Myerson)

Based on the above table, 21.6 g of Mannitol can be dissolved in 100 ml of water at 25°C while only 16.0 g of Mannitol can be dissolved in 100 ml of water at 15°C.

If the solution containing 21.6 g of Mannitol dissolved in 100ml of water is brought at 15°C, the exceeding Mannitol in solution will crystallize until the quantity of dissolved Mannitol in solution reaches 16.0 g of Mannitol in 100 ml of water, this water will also contain 5.6 g of solid Mannitol.

Baxter Mannitol solutions contain Mannitol dissolved into Water; e.g. 20% Mannitol contains 200 g Mannitol per liter of solution (equivalent to 23,3 g Mannitol in 100 g Water) and 15% Mannitol solution contain 150 g Mannitol per liter of solution (equivalent to 16,7 g Mannitol in 100 g Water).

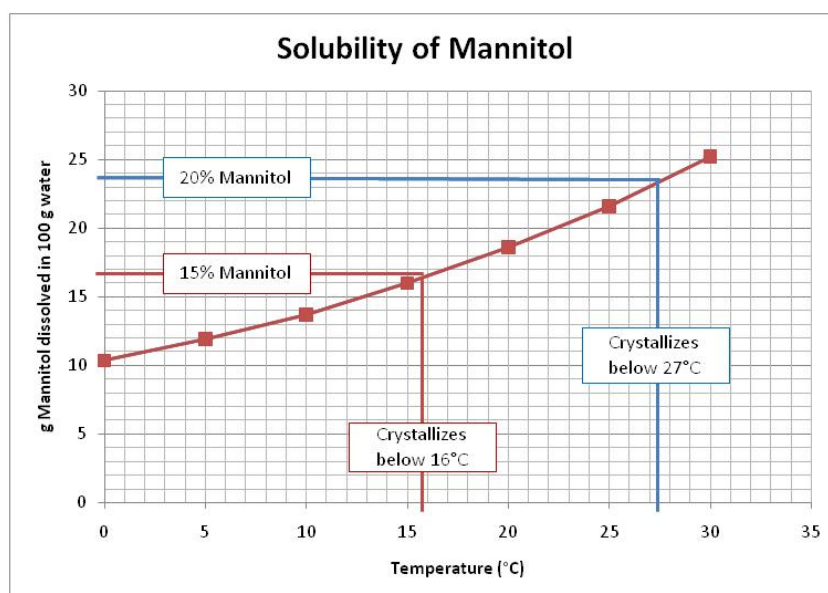


Figure 1

Based on the table and the curve shown in figure 1:

- a solution containing 20% w/v Mannitol will show no crystal when maintained at a temperature above 27°C and will start to form crystals when the temperature will decrease below this value.
- A solution containing 15% w/v Mannitol will stay crystal free (Mannitol is completely dissolved and stays in solution) when maintained above 16-17°C. It will start to form crystals when the temperature will decrease below this value and if the temperature keeps decreasing, the quantity of crystals will increase.

This crystallisation phenomenon is reversible meaning that if the temperature is increased again some crystallization will dissolve again either completely or incompletely.

Mannitol solutions are sterilized and packed in Viaflo containers; the sterilization process and used packaging may also play a role on the crystallization temperature and kinetics, however their impact is unknown and is not debated.

In conclusion, 15% Mannitol solutions have the (physico-chemical) advantage over 20% Mannitol solutions that they will be free of crystallization of Mannitol when handled at room temperature.

### References

1. Seidell. *Solubility of Organic Compounds*. 1941.
2. Yi, Y., D. Hatzivramidis, and S. A. Myerson. "Development of a Small-Scale Automated Solubility Measurement Apparatus." *Industrial & Engineering Chemistry Research* 44 (2005): 5427-33.