




## SGLT2 Inhibitors

SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS			
Reversibly inhibit sodium-glucose co-transporter-2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.			
DRUG	NOTES	FORMULARY CHOICE	PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS
<p>Empagliflozin (Jardiance®▼)</p>  <p><b>Cost per month (Dec 2015):</b> 10mg or 25mg daily £36.59</p>	<p>Empagliflozin has a cardio-protective effect – see the cardiovascular outcome study (EMPA-REG OUTCOME, Zinman et al. N Engl J Med 2015; 373:2117-2128)</p> <p>The RCT took place over a median time of 3.1 years. In patients taking empagliflozin there was a:</p> <ul style="list-style-type: none"> <li>• 38% relative risk reduction in death from cardiovascular causes</li> <li>• 35% relative risk reduction in hospitalisation for heart failure</li> <li>• 32% relative risk reduction in death from any cause</li> <li>• No significant differences between the groups for MI or stroke</li> </ul> <p>The difference between the control and treated groups began to appear after only 3 months. Whilst this is probably a class effect, empagliflozin is the only SGLT2i with published evidence of benefit and, until similar benefits are confirmed for other drugs in the class, should be the SGLT2i of choice.</p> <p><b>Use in accordance with <a href="#">NICE TA336</a>:</b></p> <p><b>Dual therapy: Met + Empagliflozin</b> <i>Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:</i></p> <ul style="list-style-type: none"> <li>• a sulfonylurea is contraindicated or not tolerated or</li> <li>• the person is at significant risk of hypoglycaemia</li> </ul>	<p>First choice</p>	<p>No long term safety data available.</p> <p><b>Empagliflozin:</b> No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk of volume depletion should be taken into account. In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.</p> <p><b>Renal impairment (eGFR or CrCl, SPC):</b></p> <ul style="list-style-type: none"> <li>• 60-89ml/min – no dose adjustment.</li> <li>• &lt;60ml/min – do not initiate empagliflozin. Max dose 10mg daily if eGFR or CrCl persistently falls below 60ml/min whilst on empagliflozin.</li> <li>• &lt;45 ml/min- discontinue empagliflozin if eGFR or CrCl</li> <li>• persistently falls below 45ml/min whilst on empagliflozin</li> </ul> <p><b>Dapagliflozin:</b> Licensed for initiation in adults between 18 and 75 years only. Not recommended for use in moderate to severe renal impairment (GFR &lt; 60 ml/min). See table on page 13.</p> <p>While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone.</p>

	<p>or its consequences.</p> <p><b>Triple therapy: Met + (Glic or Pio) + Empagliflozin</b>  <i>Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:</i></p> <ul style="list-style-type: none"> <li>• metformin and a sulfonylurea or</li> <li>• metformin and a thiazolidinedione.</li> </ul> <p><b>Empagliflozin + insulin:</b>  <i>Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.</i></p> <p><b>Licensed in combination with:</b>  other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.</p>		<p><b>Canagliflozin:</b>  Licensed for adults aged over 18 years only. For patients over 65 years, renal function and risk of volume depletion should be taken into account.</p> <p><b>Renal impairment (eGFR or CrCl, SPC):</b></p> <ul style="list-style-type: none"> <li>• 60-89ml/min – no dose adjustment.</li> <li>• &lt;60ml/min – do not initiate canagliflozin. Max dose 100mg daily if eGFR or CrCl persistently falls below 60ml/min whilst on canagliflozin.</li> <li>• &lt;45 ml/min- discontinue canagliflozin if eGFR or CrCl persistently falls below 45ml/min whilst on canagliflozin.</li> </ul> <p><b>All SGLT2 inhibitors:</b>  Due to their mechanism of action, patients taking SGLT2 inhibitors are at <b>increased risk of urinary tract infection and will test positive for glucose in their urine.</b></p> <p>SGLT2 inhibitors Increase diuresis associated with a modest decrease in blood pressure (more pronounced in patients with very high blood glucose concentrations). Not recommended for patients receiving loop diuretics or who are volume depleted (eg due to acute illness such as gastrointestinal illness). <b>Do not give SGLT2 inhibitors</b> to patients with some forms of monogenic diabetes (eg HNF1A), because of the low renal threshold for glucose in these patients and the <b>risk of severe dehydration.</b></p> <p><b>Serious and life-threatening cases of diabetic ketoacidosis (DKA)</b> have been reported in people taking SGLT2 inhibitors or shortly after stopping them. <a href="#">MHRA guidance (2015)</a> advises testing for raised ketones in people with symptoms of DKA even if plasma glucose levels are near normal. A European Medicines Agency alert (<a href="#">EMA 2016</a>) identifies a number of risk</p>
<p>Dapagliflozin (Forxiga®▼)</p> <p></p> <p><b>Cost per month (Dec 2015):</b>  10mg daily  £36.59</p>	<p>Cardiovascular outcome study (DECLARE-TIMI58) due to report in 2018</p> <p><b>Use in accordance with <a href="#">NICE TA288</a>:</b></p> <p><b>Dual therapy: Met + Dapagliflozin (as per gliptins)</b>  <i>Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for gliptins in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87).</i></p> <p><b>Dapagliflozin + insulin:</b>  <i>Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.</i></p> <p><b>Not recommended for triple therapy:</b>  <i>Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes, except as part of a clinical trial.</i></p>	<p>Second choice</p>	

<p>Canagliflozin (Invokana®▼)</p>  <p><b>Cost per month (Dec 2015):</b> 100mg or 300mg daily £39.20</p>	<p>Cardiovascular outcome study (CANVAS) due to report in 2017</p> <p><b>Use in accordance with <a href="#">NICE TA315</a>:</b></p> <p><b>Dual therapy: Met + Canagliflozin</b> <i>Canagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:</i></p> <ul style="list-style-type: none"> <li>• <i>a sulfonylurea is contraindicated or not tolerated or</i></li> <li>• <i>the person is at significant risk of hypoglycaemia or its consequences.</i></li> </ul> <p><b>Triple therapy: Met + (Glic or Pio) + Canagliflozin</b> <i>Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:</i></p> <ul style="list-style-type: none"> <li>• <i>metformin and a sulfonylurea or</i></li> <li>• <i>metformin and a thiazolidinedione</i></li> </ul> <p><b>Canagliflozin + insulin:</b> <i>Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.</i></p> <p><b>Licensed in combination with:</b> other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.</p>	<p>Second choice</p>	<p>factors — low insulin-producing capacity in the pancreas, a sudden drop in a patient's insulin dose, increased insulin requirement (due to illness, surgery or alcohol abuse) or conditions that can restrict food intake or lead to severe dehydration. In addition, the EMA recommends temporarily stopping SGLT2 inhibitors in patients who are undergoing major surgery or are in hospital due to serious illness.</p> <p><b>DO NOT GIVE SGLT2i's TO PEOPLE WITH TYPE 1 DIABETES</b></p>
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