Amarox

Important Safety Information About Dapagliflozin

Guide for Health Care Professionals
to minimise the risk of Diabetic Ketoacidosis (DKA)

Physician guide (Version: 02) *Oct 2023*

1. About this guide

Dapagliflozin is indicated as an adjunct to insulin in adult patients with BMI ≥ 27kg/m2 when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy. Dapagliflozin is not a substitute for insulin (and does not alter insulin sensitivity).

Please read:

- **this booklet in full AND**
- **the Summary of Product Characteristics (SmPC).**

This booklet only explains specific side effects for particular indications.

- It does not replace the Summary of Product
- Characteristics (SmPC) which contains the full prescribing information.

2. Conducting a dedicated education session

A dedicated education session must be held with each patient when initiating dapagliflozin. Patients should be informed in this dedicated education session, on the risk of DKA, how to recognise DKA risk factors, signs or symptoms, how and when to monitor ketone levels and what actions to take at elevated ketone readings. The risk of the patient experiencing a DKA will vary by individual, with some patients having a much greater risk than others. It is important the HCP and patient have a jointly agreed individual care plan for treating the patient's diabetes.

3. What Dapagliflozin is

Dapagliflozin is a sodium-glucose-co-transporter-2 (SGLT2) inhibitor.

- The recommended dose of Dapagliflozin in type 2 diabetes is 10 mg once daily.
- Dapagliflozin is not a substitute for insulin and does not alter insulin sensitivity.
- It improves both fasting and post-prandial plasma glucose levels - by reducing renal glucose reabsorption leading to urinary glucose excretion.
- The amount of glucose removed by the kidney in this way depends on the blood glucose concentration and glomerular filtration rate.
- Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia - and acts independently of insulin secretion and insulin action.
- To maintain treatment benefit, insulin therapy should be continuously optimised. It is recommended that Dapagliflozin therapy is regularly evaluated in the individual patient weighing the treatment benefit against the risks.

4. Risk of DKA in patients with type 1 diabetes

What you need to be aware of

There is a high background risk of DKA in patients with diabetes. This is because patients with diabetes mellitus are dependent on administered insulin. DKA can happen if patients do not take their insulin-or if they do not take enough insulin. The risk of DKA is increased with dapagliflozin treatment.

Patients and medical staff should both be:

- aware that if patients are treated with dapagliflozin, their glucose levels will not adequately reflect their insulin needs
  - DKA may occur in patients treated with dapagliflozin even if blood glucose levels are below 14mmol/L (250mg/dl) which is called euglycaemic DKA. Therefore, glucose monitoring must be supplemented by ketone monitoring.

The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Assess patients for DKA immediately if these symptoms occur - regardless of blood glucose level.

Findings from clinical studies

In the two placebo-controlled clinical studies of dapagliflozin in type 1 diabetes mellitus, patients were advised to monitor blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was ≥0.6mmol/L. In the pooled 52-week data, events of DKA were reported in 22 patients (4.0%) in the Dapagliflozin 5mg group and 6 patients (1.1%) in the placebo group, with corresponding incidence rates per 100 patient years of 4.62 for dapagliflozin 5mg and 1.27 for placebo. Of the events of DKA in the dapagliflozin 5mg group, 6 of the 23 events occurred in patients with blood glucose in the euglycaemic range (under 14mmol/L or under 250mg/dl).

5. Minimising the risk of DKA

Before starting Dapagliflozin:
Before you start, the treatment benefits need to be weighed against the risk of DKA in each individual patient.

- Treatment with Dapagliflozin, in patients with type 2 diabetes, is restricted to adult patients with BMI ≥27 kg/m2 when insulin does not provide adequate glycaemic control despite optimal insulin therapy.
- Dapagliflozin should not be initiated in patients with risk factors that may predispose them to DKA, including:
  - Sub-optimal insulin dose or low insulin needs
  - Patients not on optimal insulin dose or who have recent issues with noncompliance or recurrent errors with insulin dosing and unlikely to maintain insulin dosing.
  - Recent or recurrent history of DKA
  - Increased insulin requirements due to acute medical illness, surgery

- Excessive alcohol consumption or illicit drug use
- Patients who insist on maintaining caloric restriction, carbohydrate restriction, ketogenic diet or who chronically under dose insulin.

- Educate eligible patients on how and when to monitor ketone levels.
  - Advise patients to obtain several baseline ketone levels over 1-2 weeks before Dapagliflozin initiation and become familiar with how their behaviours and circumstances affect their ketone levels.

At Dapagliflozin initiation:

In addition to conducting a dedicated education session:

- Ensure that the patient's BMI is ≥27kg/m2.
- Ensure that ketone levels are normal (blood beta hydroxybutyrate <0.6mmol/L or urine <1+). If ketones are elevated (blood beta hydroxybutyrate reading >0.6mmol/L or urine ketones one ≥1) treatment with Dapagliflozin should not be started until the ketone reading levels are normal.
- Ensure that the patient is able and willing to monitor ketones and has demonstrated the ability to monitor ketone levels.
- Refer the patient to the General Guidance on Ketone Monitoring in the Patient Guide and ensure they are familiar with the 'Sick-Day rules' as it applies to their individual treatment plan.
- Ensure that the patient has access to ketone testing materials and immediate access to a clinician if ketone levels are elevated.
- Advise patients to monitor ketones regularly for 1-2 weeks after Dapagliflozin initiation and individualise frequency thereafter based on the patient's behaviours and circumstances including pump use. Patients should be informed about what actions to take if ketone levels are elevated.
- The patient should be informed of how to recognise the risk factors which can predispose to ketosis (including starvation ketosis) and DKA and how to recognise signs and symptoms of DKA.
- Correct volume depletion in the patient, where required
- Optimise insulin therapy.
- In order to avoid hypoglycaemia with the first dose of Dapagliflozin a 20% reduction in the first mealtime bolus insulin may be considered. Subsequent bolus doses should be adjusted individually based on blood glucose results. No reduction in basal insulin is recommended when initiating Dapagliflozin. Subsequently, basal insulin should be adjusted based on blood glucose results. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.

Reminder that insulin infusion pump users:

- Have a higher risk of DKA.
- Should only take Forxiga if they are experienced with pump use, common trouble-shooting strategies in the event of insulin interruptions (e.g. issues with insertion site, clogged tubing, empty reservoir etc.) and use of
- supplemental insulin injections with pen or syringe as needed in case of pump failure.
- Should consider monitoring ketones 3-4 hours after changing pump materials. Patients using a pump should also check their ketones with suspected insulin interruption, regardless of blood glucose level.
- Should take insulin injections within 2 hours of unexpected high glucose/ketone values and Dapagliflozin treatment should be interrupted.

6. Minimising the risk of DKA (continued)

During Dapagliflozin treatment:

- Continuously optimise insulin therapy.
- If insulin reduction is needed to prevent hypoglycaemia - reduce the dose cautiously to avoid ketosis/DKA.
- Reassess ketone monitoring frequency according to patient lifestyle/risk factors.
- Consider recommending an increase in carbohydrate intake in circumstances where ketones are raised and glucose is normal.
- Check that the patient still has the alert card.

Glucose monitoring must continue to be supplemented by ketone monitoring.

Consider when to interrupt/stop Dapagliflozin treatment:

- In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.
- Interrupt dapagliflozin treatment:
  - In settings of reduced oral intake, such as during acute illness
  - In patients who are hospitalised for major surgical procedures or acute serious medical illness.

  Monitoring of ketones is recommended in these patients. Measurement of blood ketones is preferred to urine. Treatment with Forxiga may be restarted once the ketones values are normal and the patient's condition has stabilised.
- Consider discontinuing dapagliflozin if a marked reduction in insulin need occurs.

7. If you suspect DKA and how to treat it

If DKA is suspected:

- get the patient immediate medical attention and
- Immediately stop Dapagliflozin.

Treatment of DKA should be treated as per standard of care and may require:

- insulin
- fluid
- Extra carbohydrate - especially if blood glucose levels are not markedly raised.

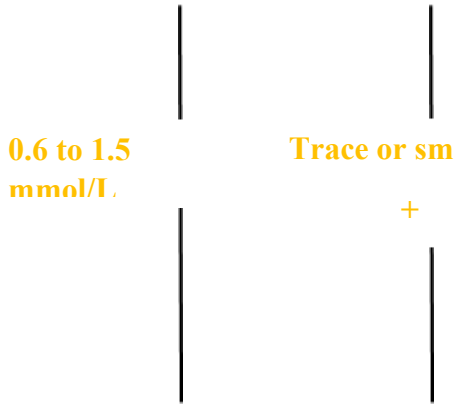
Do not stop or interrupt insulin treatment under any circumstances.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT-2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.

General Guidance on ketone monitoring

Patient should be informed about what actions to take if ketone levels are elevated. The recommended actions are listed in the diagram below

BLOOD KETONES	URINE KETONES	ACTIONS
>3.0 mmol/L	**Large to very large +++/++++**	**PROBABLE DKA** • The patient should go to emergency department without delay and stop taking dapaglifozin • The patient may need to take extra insulin and drink water. The patient should measure blood glucose and consider taking extra carbohydrates if glucose levels are normal or low
>1.5 to 3.0 mmol/L	**Moderate ++**	**IMPENDING DKA** • The patient should immediately seek medical advice and stop taking dapaglifozin. • The patient may need to take extra insulin and drink water. The patient should measure blood glucose and consider taking extra carbohydrates if the glucose levels are normal or low. • Ketone levels should be measured again after two hours.



KETONAEMIA

- The patient may need to take extra insulin and drink water. The patient should measure blood glucose and consider taking extra carbohydrates if glucose levels are normal or low.
- Ketone levels should be measured again after two hours.
- The patient should immediately seek medical advice and stop taking dapaglifozin if levels persist and symptoms present

NORMAL RANGE

- No action needed

8. Reporting Adverse Reactions

Adverse Reaction report forms are included in this Healthcare Professional Pack and should be forwarded to the Hetero Saudi at the address below. They should also be reported to the SFDA using the following:

The National Pharmacovigilance Centre
Saudi Food and Drug Authority
Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/

Saudi Amarox contact details:
Razan Almalki- Qualified Person for Pharmacovigilance
Al Jamiyah Street, Al Malaz
Riyadh code 12629, Saudi Arabia
E-mail: r.almalki@Amaroxpharma.com
Phone: +966 11 226 8850
Mobile: +966531215235

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Health Care Professional Checklist - to be completed for type 2 diabetes patients only

Before starting Dapaglifozin

- ☐ Dapaglifozin is restricted to adult patients with BMI ≥27 kg/m2 when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy
- ☐ Assess risk factors that may predispose the patient to DKA.
- ☐ Educate eligible patients on how and when to monitor blood ketones.

At Dapaglifozin initiation

- ☐ Conduct a dedicated education session with the patient in which you will:
- ☐ Give out the Patient Alert Card and Patient and Carer Guide
- ☐ Review Patient and Carer Guide with patient advising them of the following:
  - ☐ Signs or symptoms of DKA and when it can happen, emphasising that DKA may occur in patient treated with Dapagliflozin even if blood glucose levels are below 14 mmol/L (250 mg/dL).
  - ☐ How to recognise DKA risk factors
  - ☐ How to manage 'sick days'
  - ☐ When to discontinue/interrupt Dapagliflozin treatment
  - ☐ How/when to measure ketone levels and actions to be take ketosis/DKA suspected

Note: The Education Worksheet in the Patient and Carer Guide can be used to write down any guidance for patients

- ☐ Ensure the patient is able and willing to monitor ketones (blood preferred to urine)
- ☐ Ensure that ketone levels are normal
- ☐ Advise patients to monitor ketones regularly for initial 1-2 weeks of treatment and individualise frequency thereafter

- ☐ Correct volume depletion in the patient, where required
- ☐ Optimise insulin therapy
- ☐ Consider reducing the first mealtime bolus insulin by 20% with the first dose of Dapagliflozin to avoid hypoglycaemia.

Important. Do not start Dapagliflozin if ketone levels are elevated (blood ketones ≥0.6 mmol/L or urine ketones ≥1+). Wait until levels are normal.

During Dapaglifozin treatment

- ☐ Continuously optimise insulin therapy.
- ☐ If insulin reduction is needed to prevent hypoglycaemia - reduce cautiously to avoid ketosis/DKA.
- ☐ Reassess ketone monitoring frequency according to patient lifestyle/risk factors.
- ☐ Consider circumstances when Dapagliflozin needs to be stopped or interrupted.
- ☐ Check that the patient has the alert card.