PACKAGE LEAFLET

Package leaflet: Information for the user

Appref 5 mg/850 mg filmomhulde tabletten
Appref 5 mg/1000 mg filmomhulde tabletten
Appref 12,5 mg/850 mg filmomhulde tabletten
Appref 12,5 mg/1000 mg filmomhulde tabletten
empagliflozin/metformin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Appref is and what it is used for

What Appref is
Appref contains two active substances empagliflozin and metformin. Each belongs to a group of medicines called "oral anti-diabetics". These are medicines taken by mouth to treat type 2 diabetes.

What is type 2 diabetes?
Type 2 diabetes is a disease that comes from both your genes and your lifestyle. If you have type 2 diabetes, your pancreas does not make enough insulin to control the level of glucose in your blood, and your body is unable to use its own insulin effectively. This results in high levels of glucose in your blood which can lead to medical problems like heart disease, kidney disease, blindness, and poor circulation in your limbs.

How Appref works
Empagliflozin belongs to a group of medicines called sodium glucose co-transporter-2 (SGLT2) inhibitors. It works by blocking the SGLT2 protein in your kidneys. This causes blood sugar (glucose) to be removed in your urine. Metformin works in a different way to lower blood sugar levels, mainly by blocking glucose production in the liver.

Thereby this treatment lowers the amount of sugar in your blood. This medicine can also help prevent heart disease.

What Appref is used for
- Appref is added to diet and exercise to treat type 2 diabetes in adult patients and children aged 10 years and older whose diabetes cannot be controlled by adding metformin alone or metformin with other medicines for diabetes.
- This treatment can also be combined with other medicines for the treatment of diabetes. These may be medicines taken by mouth or given by injection such as insulin.

- In addition, this medicine can be used as an alternative to taking both empagliflozin and metformin as single tablets. To avoid overdose, do not continue taking empagliflozin and metformin tablets separately, if you are taking this medicine.

It is important that you continue with your diet and exercise plan as told by your doctor, pharmacist or nurse.

2. What you need to know before you take Appref

Do not take Appref
- if you are allergic to empagliflozin, metformin or any of the other ingredients of this medicine (listed in section 6);
- if you have uncontrolled diabetes, with, for example, severe hyperglycaemia (very high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see 'Risk of lactic acidosis' below) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell;
- if you have had a diabetic pre-coma;
- if you have serious kidney problems. Your doctor may limit your daily dose or ask you to take a different medicine (see also section 3, 'How to take Appref').
- if you have a severe infection such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions');
- if you have lost a lot of water from your body (dehydration), e.g. due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions');
- if you are treated for acute heart failure or have recently had a heart attack, have severe problems with your circulation (such as shock) or have breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis (see section 'Warnings and precautions');
- if you have problems with your liver;
- if you drink large amounts of alcohol, either every day or only from time to time (see section "Appref with alcohol").

Warnings and precautions
Risk of lactic acidosis
Empagliflozin/metformin may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart diseases).

If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Appref for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking Appref and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma. Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness

- difficulty in breathing
- reduced body temperature and heartbeat

Talk to your doctor promptly for further instructions
- if you are known to suffer from a genetically inherited disease affecting mitochondria (the energy-producing components within cells) such as MELAS syndrome (Mitochondrial Encephalopathy, myopathy, Lactic acidosis and Stroke-like episodes) or Maternal inherited diabetes and deafness (MIDD).
- if you have any of these symptoms after starting metformin: seizure, declined cognitive abilities, difficulty with body movements, symptoms indicating nerve damage (e.g. pain or numbness), migraine and deafness.

Lactic acidosis is a medical emergency and must be treated in a hospital.

Talk to your doctor, pharmacist or nurse before taking this medicine, and during treatment:
- if you experience rapid weight loss, feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, contact a doctor or the nearest hospital straight away and stop taking this medicine until further advice from your doctor. These symptoms could be a sign of "diabetic ketoacidosis" – a rare, but serious, sometines life-threatening problem you can get with diabetes because of increased levels of "ketone bodies" in your urine or blood, seen in tests. The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness;
- if you have "type 1 diabetes" – this type usually starts when you are young and your body does not produce any insulin. You should not take this medicine if you have type 1 diabetes;
- might be at risk of dehydration, for example:
  - if you are being sick, have diarrhoea or fever, or if you are not able to eat or drink o if you are taking medicines that increase urine production [diuretics] or lower blood pressure
  - if you are 75 years old or older.

  Possible signs are listed in section 4 under 'dehydration'. Your doctor may ask you to stop taking this treatment until you recover to prevent loss of too much body fluid. Ask about ways to prevent dehydration.

- if you have a serious infection of the kidney or the urinary tract with fever. Your doctor may ask you to stop taking this treatment until you have recovered;
- if you need to undergo an examination with iodination contrast agents (such as X-ray or scan). More information is given below in "Other medicines and Appref".

Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier´s gangrene which destroys the tissue under the skin. Fournier's gangrene has to be treated immediately.

Surgery
If you need to have major surgery you must stop taking this medicine during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with empagliflozin/metformin tablets.

Kidney function
During treatment with empagliflozin/metformin, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Foot care
Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.

Urine glucose
Because of how this medicine works, your urine will test positive for sugar while you are taking this medicine.

Children and adolescents
Appref can be used in children aged 10 years and older for the treatment of type 2 diabetes mellitus. Due to limited data caution is recommended when used in children aged between 10 and 12 years. No data are available in children below 10 years of age.

Other medicines and Appref
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking this medicine before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with empagliflozin/metformin tablets.

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of this treatment. It is especially important to mention the following:
- medicines which increase urine production (diuretics), as this medicine may increase the risk of losing too much fluid. Your doctor may ask you to stop taking empagliflozin/metformin tablets. Possible signs of losing too much fluid from your body are listed in section 4.
- other medicines that lower the amount of sugar in your blood such as insulin or a "sulphonylurea" medicine. Your doctor may want to lower the dose of these other medicines, to prevent your blood sugar levels from getting too low (hypoglycaemia).
- medicines that may change the amount of metformin in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole, crizotinib, olaparib).
- bronchodilators (beta-2 agonists) which are used to treat asthma.
- corticosteroids (given by mouth, as an injection, or inhaled), which are used to treat inflammation in diseases like asthma and arthritis.
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib).
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists).
- medicines that contain alcohol (see section 'Appref with alcohol').
- iodinated contrast agents (medicines used during an X-ray, see section 'Warnings and precautions'.
- if you are taking lithium because empagliflozin/metformin therapy can lower the amount of lithium in your blood.

Appref with alcohol
Avoid excessive alcohol intake while taking this medicine since this may increase the risk of lactic acidosis (see section 'Warnings and precautions').

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take this medicine if you are pregnant. It is unknown if this medicine is harmful to the unborn child.

Metformin passes into human milk in small amounts. It is not known whether empagliflozin passes into human breast milk. Do not take this treatment] if you are breast-feeding.

Driving and using machines
Appref has minor influence on the ability to drive and use machines.

Taking this medicine in combination with medicines called sulphonylureas or with insulin can cause blood sugar levels to drop too low (hypoglycaemia), which may cause symptoms such as shaking, sweating and change in vision, and may affect your ability to drive and use machines. Do not drive or use any tools or machines if you feel dizzy while taking Appref.

Appref contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, therefore it is considered essentially 'sodium-free'.

3. How to take Appref

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The dose of empagliflozin/metformin varies depending on your condition and the doses of diabetes medicines you currently take. Your doctor will adjust your dose as necessary and tell you exactly which strength of the medicine to take.

The recommended dose is one tablet twice a day. Your doctor will normally start this treatment by prescribing the strength of tablet that supplies the same dose of metformin you are already taking (850 mg or 1 000 mg twice a day), and the lowest dose of empagliflozin (5 mg twice a day). If you are already taking both medicines separately, your doctor will start treatment with tablets of Appref that will supply the same amount of both. If you have reduced kidney function, your doctor may prescribe a lower dose or decide to use an alternative medicine.

Taking this medicine
- Swallow the tablet whole with water.
- Take the tablets with meals to lower your chance of an upset stomach.
- Take the tablet twice daily by mouth.

Your doctor may prescribe this medicine together with another diabetes medicine. Remember to take all medicines as directed by your doctor to achieve the best results for your health. Your doctor may need to adjust your doses to control your blood sugar.

Appropriate diet and exercise help your body use its blood sugar better. It is important to stay on the diet and exercise program recommended by your doctor while taking this medicine.

If you take more Appref than you should
If you take more Appref tablets than you should have, you may experience lactic acidosis. Symptoms of lactic acidosis are non-specific such as feeling or being very sick, vomiting, stomach ache with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heartbeat. **If this happens to you, you may need immediate hospital treatment, as lactic acidosis can lead to coma. Stop taking this medicine immediately and contact a doctor or the nearest hospital straight away (see section 2).**
Take the medicine pack with you.

If you forget to take Appref
If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of this medicine.

If you stop taking Appref
Do not stop taking this treatment without first consulting your doctor, unless you suspect you have diabetic ketoacidosis, lactic acidosis, or if you have a condition that may be associated with dehydration (see section 2 "warnings and precautions"). Your blood sugar levels may increase when you stop taking empagliflozin/metformin tablets.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:
Severe allergic reaction, seen with uncommon frequency (may affect up to 1 in 100 people)
Possible signs of severe allergic reaction may include:
- swelling of the face, lips, mouth, tongue, or throat that may lead to difficulty breathing or swallowing)

Lactic acidosis, seen very rarely (may affect up to 1 in 10 000 people)
Empagliflozin/metformin may cause a very rare but very serious side effect called lactic acidosis (see section 2). If this happens you must **stop taking Appref and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

Diabetic ketoacidosis, seen rarely (may affect up to 1 in 1 000 people)
These are the signs of diabetic ketoacidosis (see section 2):
- increased levels of "ketone bodies" in your urine or blood
- rapid weight loss
- feeling sick or being sick
- stomach pain
- excessive thirst
- fast and deep breathing
- confusion
- unusual sleepiness or tiredness
- a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat.

This may occur regardless of blood glucose level. Your doctor may decide to temporarily or permanently stop your treatment with Appref.

Contact your doctor as soon as possible if you notice the following side effects:
Low blood sugar (hypoglycaemia), seen very commonly (may affect more than 1 in 10 people)
If you take this treatment with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is increased. The signs of low blood sugar may include:
- shaking, sweating, feeling very anxious or confused, fast heart beat
- excessive hunger, headache

Your doctor will tell you how to treat low blood sugar levels and what to do if you get any of the signs above. If you have symptoms of low blood sugar, eat glucose tablets, a high sugar snack or drink fruit juice. Measure your blood sugar if possible and rest.

Urinary tract infection, seen commonly (may affect up to 1 in 10 people)
The signs of urinary tract infection are:
- burning sensation when passing urine
- urine that appears cloudy
- pain in the pelvis, or mid-back pain (when kidneys are infected)

An urge to pass urine or more frequent urination may be due to the way Appref works, but they can also be signs of urinary tract infection. If you note an increase in such symptoms, you should also contact your doctor.

Dehydration, seen uncommonly (may affect up to 1 in 100 people)
The signs of dehydration are not specific, but may include:
- unusual thirst
- lightheadedness or dizziness upon standing
- fainting or loss of consciousness

Other side effects while taking Appref:
Very common
- feeling sick (nausea), vomiting
- diarrhoea or stomach ache
- loss of appetite

Common
- genital yeast infection (thrush)
- passing more urine than usual or needing to pass urine more often
- itching
- rash or red skin – this may be itchy and include raised bumps, oozing fluid or blisters
- changes to the way things taste
- thirst
- blood tests may show an increase in blood fat (cholesterol) levels in your blood
- constipation
- decreased or low vitamin B12 levels in the blood (symptoms may include extreme tiredness (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin). Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.

Uncommon
- hives
- straining or pain when emptying the bladder
- blood tests may show a decrease in kidney function (creatinine or urea)
- blood tests may show increases in the amount of red blood cells in your blood (haematocrit)

Rare
- necrotising fasciitis of the perineum or Fournier´s gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus

Very rare
- abnormalities in liver function tests, inflammation of the liver (hepatitis)
- redness of the skin (erythema)
- inflammation of the kidneys (tubulointerstitial nephritis)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Appref

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after 'EXP'. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not use this medicine if you notice that the packaging is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Appref contains
The active substances are empagliflozin and metformin.
Each Appref 5 mg/850 mg film-coated tablet (tablet) contains 5 mg empagliflozin and 850 mg metformin hydrochloride.
Each Appref 5 mg/1 000 mg film-coated tablet (tablet) contains 5 mg empagliflozin and 1 000 mg metformin hydrochloride.
Each Appref 12.5 mg/850 mg film-coated tablet (tablet) contains 12.5 mg empagliflozin and 850 mg metformin hydrochloride.
Each Appref 12.5 mg/1 000 mg film-coated tablet (tablet) contains 12.5 mg empagliflozin and 1 000 mg metformin hydrochloride.

The other ingredient(s) are:
- Tablet core: maize starch; cellulose, microcrystalline; croscarmellose sodium; hydroxypropylcellulose; silica, colloidal anhydrous; magnesium stearate
- Film coating: poly(vinyl alcohol) parial hydrolyzed (E1203); talc (E553b); titanium dioxide (E171); glycerol monocaprylocaprate; sodium lauryl sulfate
  Appref 12.5 mg/850 mg and Appref 12.5 mg/1 000 mg tablets also contain iron oxide yellow (E172). Appref 12.5 mg/850 mg and Appref 5 mg/1 000 mg tablets also contain iron oxide red (E172).

What Appref looks like and contents of the pack
Appref 5 mg/850 mg are white or almost white, 22 mm*11 mm, oval biconvex, film-coated tablet with 5-850 printed on one side and unprinted on the other side.

Appref 5 mg/1 000 mg are pink, 22 mm*11 mm, oval biconvex, film-coated tablet printed 5-1 000 on one side and unprinted on the other side.

Appref 12.5 mg/850 mg are brownish orange, 22 mm*11 mm, oval biconvex, film-coated tablet with 12.5-850 printed on one side and unprinted on the other side.

Appref 12.5 mg/1 000 mg are yellow, 22 mm*11 mm, oval biconvex, film-coated tablet with 12.5-1 000 printed on one side and unprinted on the other side.

The tablets are available in PVC/PVDC-Aluminum foil blisters.

Appref 5 mg/850 mg film-coated tablets
Pack sizes:
56 film-coated tablets
60 film-coated tablets
180 film-coated tablets

Appref 5 mg/1 000 mg film-coated tablets
Pack sizes:
10 film-coated tablets

30 film-coated tablets
60 film-coated tablets

Appref 12.5 mg/850 mg film-coated tablets
Pack sizes:
56 film-coated tablets
60 film-coated tablets

Appref 12.5 mg/1 000 mg film-coated tablets
Pack sizes:
10 film-coated tablets
30 film-coated tablets
56 film-coated tablets
60 film-coated tablets
180 film-coated tablets

Not all pack sizes may be marketed in your country.

Houder van de vergunning voor het in de handel brengen en fabrikant

Vergunninghouder:
Adalvo Limited
Malta Life Science Park, Building 1, Level 4
Sir Temi Zammit Buildings
SGN 3000 San Gwann
Malta

Fabrikant:
Adalvo Limited
Malta Life Sciences Park, Building 1, Level 4
Sir Temi Zammit Buildings
SGN 3000 San Gwann
Malta

Misom Labs Limited
Malta Life Sciences Park, Ls2.01.06 Industrial Estate
SGN 3000 San Gwann
Malta

In het register ingeschreven onder:

Appref 5 mg/850 mg filmomhulde tabletten	RVG 133828
Appref 5 mg/1000 mg filmomhulde tabletten	RVG 133829
Appref 12,5 mg/850 mg filmomhulde tabletten	RVG 133830
Appref 12,5 mg/1000 mg filmomhulde tabletten	RVG 133831

This medicine is authorised in the Member States of the European Economic Area under the following names:

Iceland	Appref 5 mg/850 mg, 5 mg/ 1000 mg, 12.5 mg/ 850 mg, 12.5 mg/ 1000 mg filmuhúðaðar töflur
Netherlands	Appref 5 mg/850 mg, 5 mg/ 1000 mg, 12.5 mg/ 850 mg, 12.5 mg/ 1000 mg filmomhulde tabletten
Malta	Appref 5 mg/850 mg, 5 mg/ 1000 mg, 12.5 mg/ 850 mg, 12.5 mg/ 1000 mg film-coated tablets

Deze bijsluiter is voor het laatst goedgekeurd in september 2025.

<Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.>