



Patient package insert according to Pharmacists' Regulations (Preparations) – 1986

This medicine can be sold without a physician's prescription

Combodex[®], Caplets

Each caplet contains:

Paracetamol 500 mg

Ibuprofen 150 mg

Inactive ingredients and allergens in the medicine - see section 6 "Additional information" and in section 2 "Important information about some of the ingredients of the medicine".

Read this entire leaflet carefully before using this medicine. This leaflet contains concise information about the medicine. If you have any further questions, ask the doctor or pharmacist.

Take this medicine according to the instructions in section 3 "How to use this medicine?" in this leaflet. Consult the pharmacist if you need additional information. Refer to a doctor if the symptoms of your illness get worse or if they do not improve after 3 days.

1. What is the medicine intended for?

Combodex is used for relief of pain such as: headache, migraine-related headache, tension headache, sinus pain, toothache, backache, sore throat, period pain, muscular pain, rheumatic pain, pain associated with dental procedures, arthritis, tennis elbow; for the relief of aches associated with colds and flu. Also intended to reduce fever.

Therapeutic group: Combodex contains paracetamol and ibuprofen. Paracetamol is a pain reliever and fever reducer. Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) it is a pain reliever and reduces inflammation (swelling, redness or soreness).

2. Before using the medicine

Do not use the medicine if:

- you are hypersensitive (allergic) to the active ingredients (paracetamol, ibuprofen), to other NSAIDs or to any of the other ingredients this medicine contains (see section 6).
- you suffer or have previously suffered from bleeding in your stomach or bowel or from bloody diarrhoea.
- you suffer or have previously suffered from a peptic ulcer (a gastrointestinal ulcer).
- you are taking other medicines which contain paracetamol or ibuprofen, high dose aspirin (above 75mg each day) or other NSAIDs including cyclo-oxygenase-2 (COX-2) specific inhibitors e.g. etoricoxib and celecoxib.
- you regularly drink large quantities of alcohol.
- you suffer from severe heart failure, hepatic failure or renal failure.
- you suffer from cerebrovascular bleeding or other active bleeding.
- you suffer from blood-clotting disturbances (i.e. reduced numbers of platelets in the blood).
- you have suffered from asthma, urticaria or allergic reactions after taking aspirin/acetylsalicylic acid or other NSAIDs.
- you are in the last three months of pregnancy.

Special warnings regarding the use of the medicine

If you are taking **Combodex** for longer than the recommended time or higher than recommended dosage, you are at risk of serious harm. These include serious harm to the stomach/gut and kidneys, as well as very low levels of potassium in your blood.

These can be fatal (see section 4).

- Consult a doctor or a pharmacist before taking **Combodex**.
- Anti-inflammatories and pain killers like ibuprofen may be associated with a small increased risk of heart attack or stroke, particularly when used at high doses. Do not exceed the recommended dose or duration of treatment.
- **Skin reactions**
Serious skin reactions have been reported in association with **Combodex** treatment. Stop taking this medicine and seek medical attention immediately if you develop any type of skin rash, lesions of the mucous membranes, blisters or other signs of allergy since these can be the first signs of a very serious skin reaction. See section 4.
- During treatment with the medicine, tell your doctor straight away if you have severe illnesses, including severe renal impairment, sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), you suffer from malnutrition, chronic alcoholism or if you are taking flucloxacillin (an antibiotic). A serious condition called metabolic acidosis (a blood and fluid abnormality) has been reported in patients in these situations when paracetamol is used at regular dose for a prolonged period or when paracetamol is taken together with flucloxacillin. Symptoms of metabolic acidosis may include: serious breathing difficulties with deep rapid breathing, drowsiness, nausea and vomiting.

Before treatment with Combodex, tell the doctor or pharmacist if:

- you suffer from heart problems including heart failure, angina (chest pain), or if you have had a heart attack, bypass surgery, peripheral artery disease (poor circulation in the legs or feet due to narrow or blocked arteries), or any kind of stroke (including "mini-stroke" or transient ischemic attack "TIA").
- you suffer from high blood pressure, diabetes, high cholesterol, have a family history of heart disease or stroke, or if you are a smoker.
- you suffer from liver disease, hepatitis, kidney disease or difficulty urinating.
- you are a drug user or a heavy alcohol drinker.
- you are pregnant or plan to become pregnant.
- you are breastfeeding or plan to breastfeed.
- you currently suffer from an infection.
Taking **Combodex** may mask signs of infection such as fever and pain. Therefore, taking **Combodex** may delay receiving suitable treatment for infection, which may lead to an increased risk for complications. This effect has been observed in lung infection caused by bacteria and bacterial skin infections related to chicken pox. If you are taking the medicine while suffering from infection and the symptoms of infection persist or worsen, consult the doctor as soon as possible.
- you plan to undergo surgery.
- you are over the age of 65.
- you suffer or have previously suffered from other medical conditions including:
 - heartburn, indigestion, stomach ulcer or any other stomach problems.
 - vomiting blood or rectal bleeding.
 - asthma.

- vision problems.
 - tendency to bleed or other blood system problems.
 - intestinal problems such as ulcerative colitis or Crohn's Disease.
 - swelling of the ankles or feet.
 - diarrhea.
 - inherited genetic or acquired disorder of certain enzymes that manifest with either neurological complications or skin problems or occasionally both i.e. porphyria.
 - smallpox.
 - autoimmune disease such as Lupus erythematosus.
- The medicine contains ibuprofen that belongs to a group of medicines (NSAIDs) which may impair the fertility in women. This effect is reversible upon stopping the treatment.
 - Taking this medicine may interfere with the results from the urine analysis test for 5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. To avoid false results do not take this medicine or other paracetamol containing medicines for several hours before or during the collection of the urine sample.

Children and adolescents

The medicine is intended for adults and children over the age of 12.

Drug interactions

If you are taking, have recently taken or might take other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

Especially if you are taking:

- anticoagulants (medicines to thin blood/prevent clotting e.g. aspirin/acetylsalicylic acid, warfarin, ticlopidine).
- medicines to treat epilepsy or fits such as phenytoin.
- chloramphenicol (an antibiotic used to treat ear and eye infections).
- probenecid, a medicine for the treatment of gout.
- zidovudine, a medicine for the treatment of HIV (a virus that causes AIDS).
- medicines for the treatment of tuberculosis such as isoniazid.
- aspirin/acetylsalicylic acid, salicylates or other NSAID medicines.
- medicines that reduce high blood pressure (ACE inhibitors such as captopril, beta-blockers such as atenolol, angiotensin-II receptor antagonists such as losartan).
- medicines for the treatment of other heart conditions such as digoxin.
- diuretics.
- lithium, a medicine used to treat certain types of depression.
- methotrexate, a medicine used to treat arthritis and certain types of cancer.
- corticosteroids, such as prednisone, cortisone.
- metoclopramide, propantheline.
- tacrolimus or ciclosporin, immunosuppressives used after organ transplant.
- sulphonylurea, a medicine for the treatment of diabetes.
- certain antibiotics (such as quinolone antibiotics).
- medicines used to treat depression e.g. SSRIs (selective serotonin-reuptake inhibitors).
- mifepristone, a medicine used for medical termination of a pregnancy.
- flucloxacillin (antibiotic), due to a serious risk of blood and fluid abnormality (called metabolic acidosis) that must be treated urgently. (See in section 2 "Special warnings regarding the use of the medicine").

These medicines may be affected by **Combodex** or may affect the way **Combodex** works.

You may need to take different dosages of your medicines, or you may need to take different medicines. Some other medicines may also affect or be affected by the treatment with **Combodex**.

You should therefore always consult your doctor or pharmacist before using **Combodex** with other medicines. Your doctor or pharmacist will have more information on these and other medicines to be careful with or avoid while taking this medicine.

Use of the medicine and food

Swallow the medicine with a full glass of water, with or without food.

Use of the medicine and alcohol consumption

Do not consume alcoholic beverages while taking the medicine. Mixing alcohol with other medicines may cause liver damage.

Pregnancy, breast-feeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, consult a doctor or pharmacist before using this medicine.

Do not take the medicine in the last 3 months of pregnancy, as it could harm your unborn child or cause problems at delivery. It can cause kidney and heart problems in your unborn baby. It may affect your or your baby's tendency to bleed and cause labour to be later than expected. If you are in the first 6 months of your pregnancy, you should only take the medicine if absolutely necessary and advised by your doctor. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used.

If taken for more than a few days from 20 weeks of pregnancy onward, **Combodex** can cause kidney problems in your unborn baby that may lead to low levels of amniotic fluid or narrowing of a blood vessel in the heart of the baby (ductus arteriosus). If you need treatment for longer than a few days, your doctor may recommend additional monitoring.

This medicine may impair female fertility and is not recommended in women attempting to conceive.

Driving and using machines

Be careful when driving or operating machines until you know how the medicine affects you. As for children, they should be warned about riding a bicycle or playing near roads etc.

Important information about some of the ingredients of the medicine

Combodex contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per caplet, that is to say, essentially "sodium-free".

3. How to use the medicine?

Check with the doctor or pharmacist if you are not sure about the dosage and the manner of treatment with the medicine.

The usual dosage for adults and children over the age of 12 years:

1-2 caplets every 6 hours, as required. Do not take more than 8 caplets in 24 hours.

Take the lowest effective dose for the shortest time necessary to achieve the treatment

objective. Consult a doctor if the symptoms worsen or do not improve, or if you need to take the medicine for more than 3 days.

Do not exceed the recommended dose.

If your doctor prescribed a different dose, follow the doctor's directions.

Method of administration

Swallow the medicine with a full glass of water with or without food.

For ease of swallowing, if necessary, the caplet may be divided for immediate use. Swallow the two parts together immediately after division.

Do not crush or chew the caplets to avoid the bitter taste of the medicine.

If you have accidentally taken a higher dosage

If you have accidentally taken an overdose or if a child has accidentally swallowed the medicine, proceed immediately to a doctor or a hospital emergency room and bring the package of the medicine with you, to get an opinion of the risk and advice on action to be taken. Do this even if there are no signs of discomfort or poisoning.

Taking an overdose of **Combodex** can lead to delayed serious liver and renal damage. You may need urgent medical attention.

The symptoms can include nausea, stomach pain, vomiting (may be blood streaked), headache, ringing in the ears, confusion and shaky eye movement. At high doses, drowsiness, chest pain, palpitations, loss of consciousness, convulsions (mainly in children), weakness and dizziness, blood in urine, cold body feeling, and breathing problems have been reported.

If you forgot to take the medicine

If you forgot to take this medicine at the designated time, take a dose as soon as you remember, unless it is almost time for your next dose; skip the forgotten dose and take the next dose at the regular time.

Do not take a double dose to make up for a forgotten dose.

If you are not sure whether to skip the dose, consult the doctor or pharmacist.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have further questions on the use of this medicine, consult the doctor or pharmacist.

4. Side effects

Like any medicine, the use of **Combodex** may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Stop taking this medicine and refer to the doctor or to a hospital emergency room immediately with the occurrence of:

- **fever, generally feeling unwell, nausea, stomach ache, headache and stiff neck.**
- **vomiting blood or particles that look like coffee grounds.**
- **rectal bleeding, black sticky bowel motions (stools) or bloody diarrhoea.**
- **swelling of the face, lips or tongue which may cause difficulty in swallowing or breathing.**
- **asthma, wheezing, shortness of breath.**

- very rare cases of serious skin reactions have been reported including sudden or severe itching, skin rash, hives.
- severe blisters and bleeding in the lips, eyes, mouth, nose and genitals (Stevens-Johnson Syndrome).
- a severe skin reaction known as Hypersensitivity Syndrome (DRESS), the symptoms include: skin rash, fever, swelling of lymph nodes and an increase of eosinophils (a type of white blood cells).

Combodex, especially when taken at higher than recommended doses or for a prolonged period of time, can cause damage to your kidneys and affect them removing acids properly from your blood into the urine (renal tubular acidosis). It can also cause very low levels of potassium in your blood (see section 2). This is a very serious condition and will require immediate treatment. Signs and symptoms include muscle weakness and light-headedness.

Additional side effects:

Common side effects (effects that occur in 1-10 out of 100 users):

- fluid retention, swelling
- ringing in the ears (tinnitus)
- nausea or vomiting, loss of appetite, heartburn or pain in the upper part of your stomach, diarrhoea
- skin rashes
- headache, dizziness
- changes in liver or kidney function (determined by blood tests)
- irritability

Uncommon side effects (effects that occur in 1-10 out of 1,000 users):

- reduction in red blood cells, bleeding episodes such as nosebleed, abnormal or prolonged bleeding during menstrual periods, an increased number of platelets
- eye problems such as blurred or diminished vision, changes to the appearance of colours
- wind (gas) and constipation
- an increased sensitivity to allergic reactions, angioedema (the symptoms can include itchy, red, painful eyes)
- breast enlargement (in men)
- abnormally low sugar level (hypoglycaemia)
- changes in mood, for example depression, confusion, excessive emotional reactions
- changes in the desire to sleep (sleepiness or sleeplessness)
- difficulty urinating
- thickening of respiratory secretions (mucous)

Rare side effects (effects that occur in 1-10 out of 10,000 users):

- hallucinations and increased nightmare occurrence
- numbness or abnormal skin sensations (e.g., burning, tingling, or pricking) in the hands and feet

Very rare side effects (effects that occur in less than 1 in 10,000 users):

- severe pain or tenderness in the stomach.
- signs of frequent or worrying infections such as fever, severe chills, sore throat or mouth ulcers.
- a tendency to bleed or bruise more easily than normal, reddish or purplish blotches under the skin.
- signs of anaemia, such as tiredness, headaches, shortness of breath, paleness.

- vertigo.
- yellowing of the skin and/or eyes, jaundice.
- unusual weight gain, swelling of the ankles or legs, decreased urine output.
- involuntary muscle movements/spasms, tremors and convulsions, slowing of physical and emotional responses.
- temporary vision loss, pain during eye movement.
- symptoms of sunburn (such as redness, itching, swelling, blistering) which may occur more quickly than normal.
- fast or irregular heartbeats (palpitations).
- increased sweating.

Side effects with unknown frequency (effects for which a frequency has not yet been determined):

- A red, scaly widespread rash with bumps under the skin and blisters located mainly on the skin folds, trunk, and upper extremities accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis). Stop the use of the medicine if you develop these symptoms and seek medical attention immediately (see also section 2).
- A serious condition that can make blood more acidic (metabolic acidosis), in patients with severe illness using paracetamol (see section 2).

The above list includes serious side effects that may require medical attention. Serious side effects are rare for low doses of this medicine and when used for a short period of time.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health by clicking the link "דיווח על תופעות לוואי עקב טיפול תרופתי" found on the homepage of the Ministry of Health website (www.health.gov.il) directing to the online form for reporting side effects or via the link: <https://sideeffects.health.gov.il>

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine must be stored in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (תאריך תפוגה) stated on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** store below 25°C. Store in the original package to protect from light.
- Do not throw away any medicines via wastewater or household waste. Ask the pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredients, this medicine also contains:

Maize starch, pregelatinised maize starch, microcrystalline cellulose, croscarmellose sodium, talc, hypromellose methylcellulose 2910, magnesium stearate, lactose monohydrate, titanium dioxide (E171), polyethylene glycol 4000, sodium citrate dihydrate (E331).

What the medicine looks like and what the package contains:

White caplet with a score line on one side.

Approved package sizes: 2, 8, 10, 16, 20, 24, 30 caplets. Not all package sizes may be marketed.

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Drug registration number at the national drug registry of the Ministry of Health:
156-94-34420-00

Manufacturer and registration holder: Dexcel Ltd., 1 Dexcel St., Or Akiva 3060000, Israel