

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
The medicine is dispensed with a doctor's prescription only

Yuflyma
20 mg
40 mg
80 mg

Solution for injection in a pre-filled pen/syringe

Active ingredient and its concentration: adalimumab 100 mg/ml
Each 20 mg Yuflyma pre-filled syringe contains:
adalimumab 20 mg/0.2 ml

Each 40 mg Yuflyma pre-filled pen contains:
adalimumab 40 mg/0.4 ml

Each 80 mg Yuflyma pre-filled pen contains:
adalimumab 80 mg/0.8 ml

Inactive and allergenic ingredients in the preparation – see section 6 "Further information" in this leaflet.

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat your ailment/you. Do not pass it on to others. It may harm them even if it seems to you that their ailment/medical condition is similar.

Yuflyma is a biosimilar medicinal product. For additional information on biosimilar medicinal products, refer to the Ministry of Health website: <https://www.gov.il/he/Departments/General/Biosimilar>

In addition to the leaflet, Yuflyma has a "Patient safety information card". This card includes important safety information which you should know before starting and during the treatment with Yuflyma and act accordingly. Read the "Patient safety information card" and the patient leaflet before starting to use the medicinal product. Keep the card for further reading, if necessary.

Please note that it is important that each time you receive the medicine from the pharmacy you are sure that you receive the medicine that was prescribed for you by the specialist treating you. If the medicine you received looks different than the one you usually receive, or if the instructions for use have changed, please refer immediately to the pharmacist and make sure that you received the correct medicine. Any change or change in the dosage of a medicine containing adalimumab (the active ingredient in the medicine) must be made by the attending specialist only. Please check that the trade name of the medicinal product prescribed for you by the specialist in the prescription, is identical to the name of the medicine you received from the pharmacist.

1. WHAT IS THE MEDICINE INTENDED FOR?

Rheumatoid arthritis

Yuflyma in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is not appropriate.

Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Polyarticular juvenile idiopathic arthritis

Yuflyma in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients from the age of 2 years, who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years.

Enthesitis-related arthritis

Yuflyma is indicated for the treatment of active enthesitis-related arthritis, in patients 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Ankylosing spondylitis (AS)

Yuflyma is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS

Yuflyma is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS, but with objective signs of inflammation by radiological and/or laboratory tests including MRI and serum CRP levels, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).

Psoriatic arthritis

Yuflyma is indicated for the treatment of active and progressive psoriatic arthritis, in adults, when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage, as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Psoarthritis

Yuflyma is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

Paediatric plaque psoriasis

Yuflyma is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age, who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

Hidradenitis suppurativa (HS)

Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age, with an inadequate response to conventional systemic HS therapy.

Crohn's disease

Yuflyma is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease, who have had an inadequate response to conventional therapy. Yuflyma is also indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Paediatric Crohn's disease

Yuflyma is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients from 6 years of age, who have had an inadequate response to conventional therapy including primary nutrition therapy and corticosteroid and/or immunomodulator, or who are intolerant to or have contraindications for such therapies.

Ulcerative colitis

Yuflyma is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients, who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis

Yuflyma is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age), who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Uveitis

Yuflyma is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients, who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatric uveitis

Yuflyma is indicated for the treatment of chronic non-infectious uveitis in paediatric patients from 2 years of age, who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

Intestinal Behçet's disease

Yuflyma is indicated for the treatment of intestinal Behçet's disease, in patients who have had an inadequate response to conventional therapy.

Yuflyma contains the active ingredient adalimumab.

The active ingredient in Yuflyma, adalimumab, is a human monoclonal antibody.

Monoclonal antibodies are proteins that attach to specific targets. The target of adalimumab is a protein called tumor necrosis factor (TNF α), which is involved in the immune (defense) system and is present at increased levels in the inflammatory diseases listed above. By attaching to TNF α , Yuflyma reduces the inflammatory process in these diseases.

There is no information regarding use of Yuflyma in children under two years of age.

Therapeutic group: TNF blocker.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to the active ingredient, or to any of the additional ingredients included in the medicine (see section 6 "Further information").
- you have active tuberculosis or other severe infections, such as sepsis and opportunistic infections (see "Special warnings regarding use of the medicine"). It is important that you tell your doctor if you have symptoms of infection, for example fever, wounds, feeling tired and dental problems.
- you have moderate or severe heart failure. It is important to tell your doctor if you have or have had a serious heart problem (see "Special warning regarding use of the medicine").

Special warnings regarding use of the medicine

Before treatment with Yuflyma, inform your doctor:

Allergic reactions

- If you suffer from allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash, do not inject more Yuflyma and contact your doctor immediately since, in rare cases, these reactions can be life-threatening.

Infections

- If you have an infection, including prolonged infection or a localized infection (for example, leg ulcer) consult your doctor before using Yuflyma. If you are infected, refer to your doctor.
- You might get infections more easily while receiving Yuflyma treatment. This risk may increase if you have a problem with your lungs. These infections may be serious and include:
 - tuberculosis
 - infections caused by viruses, fungi, parasites or bacteria
 - severe infection in the blood (sepsis)

In rare cases, these infections can be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend that you temporarily stop treatment with Yuflyma.

- Consult your doctor if you live or travel in regions where fungal infections (for example, histoplasmosis, coccidioidomycosis) are very common.
- Consult your doctor if you have had recurrent infections or other conditions that increase the risk of infections.
- If you are over the age of 65 years, you may be more likely to get infections during treatment with Yuflyma. You and your doctor should pay special attention to signs of infection during the course of treatment with Yuflyma. It is important to tell your doctor if you have symptoms of infections, such as fever, wounds, feeling tired or dental problems.

Tuberculosis

- It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. If you have active tuberculosis, do not use Yuflyma.
- As cases of tuberculosis have been reported in patients treated with adalimumab, your doctor will check you for signs or symptoms of tuberculosis before you start Yuflyma treatment. This will include a thorough medical evaluation, including your medical history and appropriate screening tests (for example, chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your "Patient Safety Information Card".

Tuberculosis can develop during therapy, even if you have received treatment for the prevention of tuberculosis.

- If symptoms of tuberculosis (for example, persistent cough, weight loss, lack of energy, mild fever), or of any other infection appears during or after treatment with Yuflyma, refer to your doctor immediately.

Hepatitis B

- Tell your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of contracting HBV.
- Your doctor should perform an HBV test. In people who carry HBV, Yuflyma can cause its reactivation.
- In rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

Dental procedure or surgery

- If you are due to undergo dental procedures or surgery, inform your doctor that you are taking Yuflyma. Your doctor may recommend temporary discontinuation of Yuflyma.

Demyelinating diseases

- If you have or develop a demyelinating disease (a disease that affects the insulating layer around the nerves, such as multiple sclerosis), your doctor will decide if you should receive or continue to receive Yuflyma. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of the body.

Vaccinations

- Certain vaccines may cause infections and you should not receive them during the course of treatment with Yuflyma.
- Consult your doctor before you receive any vaccine.
- It is recommended that children, if possible, be given all the vaccinations scheduled for their age before starting treatment with Yuflyma.
- If you were treated with Yuflyma during pregnancy, your baby may be at higher risk for an infection for approximately five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and healthcare providers that you were treated with Yuflyma during pregnancy so they can decide when your baby can receive vaccines.

Heart failure

- If you have mild heart failure and are being treated with Yuflyma, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have or have had a serious heart problem. If new heart failure symptoms develop or if the existing symptoms worsen (e.g., shortness of breath, or swelling of the feet), refer to your doctor immediately. Your doctor will decide if you should receive Yuflyma.

Fever, bruising, bleeding or palor

- In some patients, the body fails to produce a sufficient amount of the blood cells that fight infections or that help stop bleeding. Your doctor may decide to stop treatment. If you develop a fever that does not go away, mild bruises or if you bled very easily or look very pale, refer to your doctor immediately.

Cancer

- Very rare cases of certain kinds of cancer in adults and children treated with adalimumab or other TNF blockers have been described.
- People with more serious rheumatoid arthritis who have had the disease for a long time, may be at higher than average risk of getting lymphoma (a cancer that affects the lymphatic system) and leukemia (a cancer that affects the bone marrow and the blood).

- If you are being treated with Yuflyma, the risk of getting lymphoma, leukemia, or other cancers may increase.
- On rare occasions, an uncommon and severe type of lymphoma, has been seen in patients taking adalimumab. Some of those patients were also treated with azathioprine or 6-mercaptopurine.

- Tell your doctor if you are taking azathioprine or 6-mercaptopurine together with Yuflyma.
- Cases of non-melanoma skin cancer have been observed in patients taking adalimumab.
- Tell your doctor if new skin lesions appear or if there is a change in existing lesions during or after therapy.

Cases of non-lymphoma cancers have been reported in patients who took a different TNF blocker and who have a certain type of lung disease called chronic obstructive pulmonary disease (COPD). If you have COPD, or are a heavy smoker, consult with your doctor on whether treatment with a TNF blocker is appropriate for you.

Autoimmune disease

- On rare occasions, treatment with Yuflyma could result in joint pain or tiredness occur. Refer to your doctor if symptoms such as persistent unexplained rash, fever, lump-like or tiredness occur.

Smoking

If you are a heavy smoker, consult with your attending doctor on whether treatment with a TNF blocker is appropriate for you (see additional information in section "Special warnings regarding use of the medicine").

Children and adolescents

Vaccinations: If possible, children should receive all the necessary vaccinations before starting treatment with Yuflyma.

Drug interactions

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

Do not take Yuflyma with medicines containing the following active ingredients, due to increased risk of serious infections:

- anakinra
- abatacept

These medicines are used to treat rheumatoid arthritis.

Yuflyma can be taken together with:

- methotrexate
- certain disease-modifying anti-rheumatic agents for treatment of arthritis (for example, sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations)
- steroids or pain medications, including non-steroidal anti-inflammatory drugs (NSAIDs).

If you have questions, ask your doctor.

Pregnancy and breastfeeding

- You should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last Yuflyma treatment.
- If you are pregnant, think you may be pregnant or are planning a pregnancy, consult with your doctor about taking this medicine.
- Yuflyma should only be used during a pregnancy if needed.
- In a study that assessed its use in pregnant women, there was no higher risk of birth defects when the mother had received adalimumab during pregnancy compared with mothers with the same disease who did not receive adalimumab.
- Yuflyma can be taken during breastfeeding.
- If you received Yuflyma during pregnancy, your baby may be at higher risk for developing infections.

Before your baby receives any vaccine, it is important to inform the pediatrician treating your baby, as well as the healthcare providers in the clinic and Family Health Center (Tzup Chalav), that you took Yuflyma during the pregnancy. For more information on vaccines, see section "Special warnings regarding use of the medicine".

Driving and using machinery

Yuflyma may have a negligible effect on the ability to drive, ride a bicycle or operate machinery. After treatment with Yuflyma, you may have a sensation of dizziness and visual disturbances.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicinal product according to the doctor's instructions.

Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the medicinal product. The dosage and treatment regimen will be determined by the doctor only.

Do not exceed the recommended dose.

Method of administration:

Yuflyma solution for injection in a pre-filled pen/syringe is injected under the skin (subcutaneous use). Detailed instructions on how to inject Yuflyma are provided in section 7 "Instructions for use".

If you accidentally took a higher dosage

If you accidentally injected Yuflyma more frequently than instructed by your doctor or pharmacist, call your doctor or pharmacist and report this to them. Always bring the package of the medicine with you, even if it is empty.

If you forgot to inject Yuflyma

If you forgot to inject Yuflyma, inject the next dose as soon as you remember. The next dose should be taken as originally scheduled had you not forgotten a dose. Adhere to the treatment regimen as recommended by the doctor. Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.

If you stop taking Yuflyma

Discuss discontinuation of Yuflyma with your doctor. Your symptoms may recur when you stop taking Yuflyma.

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

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

4. SIDE EFFECTS

As with any medicine, use of Yuflyma 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.

Most side effects are mild to moderate. However, some side effects may be serious and require treatment.

Side effects may occur up to at least 4 months after the last Yuflyma treatment.

Refer to your doctor immediately if you notice any of the following symptoms:

- severe rash, hives or other signs of allergic reaction
- swelling in the face, hands, feet
- breathing difficulties, swallowing difficulties
- shortness of breath with physical activity or upon lying down or swelling of the feet

Refer to your doctor as soon as possible if you notice any of the following symptoms:

- signs suggestive of infection such as fever, nausea, wounds, dental problems, burning upon urination
- feeling weak or tired
- cough
- tingling
- numbness
- double vision
- arm or leg weakness
- a bump or open sore that does not heal
- signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness

The symptoms described above can be signs of the following side effects, which have been observed with Yuflyma.

Very common side effects (effects that occur in more than 1 user in 10):

- injection site reactions (including pain, swelling, redness or itching)
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia)
- headache
- abdominal pain
- nausea and vomiting
- rash
- musculoskeletal pain

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

- serious infections (including blood poisoning and influenza)
- intestinal infections (including gastroenteritis)
- skin infections (including cellulitis, shingles)
- ear infections
- oral infections (including tooth infections and cold sores)
- reproductive tract infections
- urinary tract infection
- fungal infections
- joint infections
- benign tumors
- skin cancer
- allergic reactions (including seasonal allergy)
- dehydration
- mood swings (including depression)
- nerve root compression (including lower back pain and leg pain)
- sleeping difficulties
- sensation disorders such as sense of tingling, prickling or numbness
- migraine
- nerve root compression (including lower back pain and leg pain)
- vision disturbances
- eye inflammation
- inflammation of the eyelid and eye swelling
- vertigo (feeling of dizziness or spinning)
- sensation of rapid heart beats
- high blood pressure
- flushing
- hematoma (collection of blood outside of blood vessels)
- cough
- asthma
- shortness of breath
- gastrointestinal bleeding
- dyspepsia (indigestion, bloating, heartburn)
- acid reflux disease
- sicca syndrome (including dry eyes and dry mouth)
- itching
- itch rash
- bruising
- inflammation of the skin (such as eczema)
- breaking of fingernails and toenails
- increased sweating
- hair loss
- new onset or worsening of psoriasis
- muscle spasms
- blood in the urine
- kidney problems
- chest pain
- edema (swelling)
- fever
- reduction in blood platelets which increases the risk of bleeding or bruising
- impaired healing

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

- opportunistic infections (which include tuberculosis and other infections that occur when resistance of the body to disease is lowered)
- neurological infections (including viral meningitis)
- eye infections
- bacterial infections
- diverticulitis (infection and inflammation of the large intestine)
- cancer
- cancer that affects the lymphatic system
- melanoma
- immune system disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- inflammation of blood vessels (vasculitis)
- tremor
- disorder of the nerves (neuropathy)
- stroke
- hearing loss, buzzing
- sensation of heart beating irregularly, such as skipping a beat
- heart problems that can cause shortness of breath or ankle swelling
- heart attack
- a sac in the wall of a major artery, inflammation and clot of a vein, blockage of a blood vessel
- lung diseases causing shortness of breath (including inflammation)
- pulmonary embolism (blockage in an artery of the lung)
- seroma (collection of fluid in the pleural space (pleural effusion))
- inflammation of the pancreas which causes severe pain in the abdomen and back
- difficulty in swallowing
- facial edema (swelling of the face)
- gallbladder inflammation, gallbladder stones
- fatty liver
- night sweats
- scarring
- abnormal breakdown of muscle tissue
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems)
- sleep interruptions
- impotence
- inflammations

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

- leukemia (cancer affecting the blood and bone marrow)
- severe allergic reaction with shock
- multiple sclerosis
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body)
- heart stops pumping
- scarring of the lung (pulmonary fibrosis)
- intestinal perforation (hole in the intestine)
- hepatitis
- reactivation of hepatitis B
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- inflammation of blood vessels in the skin (cutaneous vasculitis)
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash)
- facial edema (swelling of the face) associated with allergic reactions
- erythema multiforme (inflammatory skin rash)
- lupus-like syndrome
- angioedema (localized swelling of the skin)
- itchy red skin reaction (itchy reddish-purple skin rash)

Side effects of unknown frequency (the frequency can not be estimated from the available data):

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal)
- Merkel cell carcinoma (a type of skin cancer)
- Kaposi's sarcoma, a type of cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin
- liver failure
- worsening of dermatomyositis (looks like a skin rash accompanied by muscle weakness)
- weight gain (most patients had a minor weight gain)

Some of the side effects, observed when using the medicinal product, have no symptoms and can only be detected by blood tests. These include:

Very common side effects (effects occurring in more than 1 user in 10):

- low levels of white blood cells
- low levels of red blood cells
- decreased lipids in the blood
- elevated liver enzymes

Common side effects (effects occurring in 1-10 in 100 users):

- high levels of white blood cells
- low levels of platelets
- increased uric acid in the blood
- abnormal levels of sodium in the blood
- low levels of calcium in the blood
- low levels of phosphate in the blood
- high blood sugar
- high levels of the lactate dehydrogenase enzyme in the blood
- presence of autoantibodies in the blood
- low levels of potassium in the blood

Uncommon side effects (effects occurring in 1-10 in 1,000 users):

- high bilirubin values (liver function blood test)