meto ject® | metex®

KEY FACTS

Content

metoject®/metex® PEN characteristics

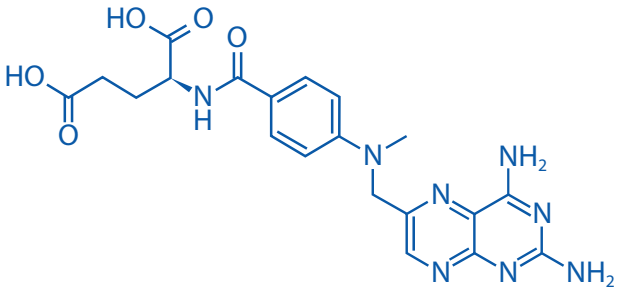
Qualitative composition

- Pre-filled pen with solution containing methotrexate

Pharmaceutical form

- Solution for injection in pre-filled pen
- Clear, yellow-brown solution

Methotrexate (active ingredient)



Excipients included in the composing

- Sodium chloride
- Sodium hydroxide (for pH adjustment)
- Hydrochloric acid (for pH adjustment)
- Water for injections

Pharmacodynamic properties

- Pharmacotherapeutic group: Folic acid analogues

Autoinjector

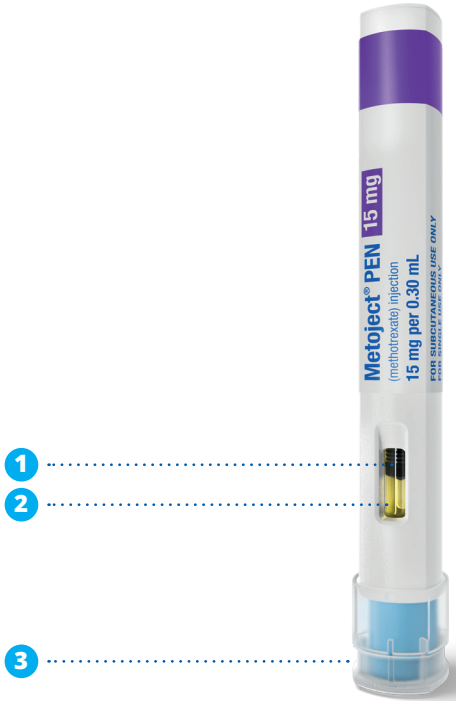
Introduction

metoject®/metex® PEN is a pre-filled autoinjector with various available doses of the active ingredient methotrexate in a concentration of 50 mg/ml.

Furthermore, the pre-filled pen contains a colorless pre-filled syringe (glass) with a plunger stopper (chlorobutyl rubber) and embedded injection needle. The syringe is externally equipped with the device for self-administration (pen).

Appearance and key elements

1. **Plunger**
2. **Inspection window**
3. **Protective cap**



Autoinjector

Indications

metoject®/metex® PEN is indicated or the treatment of

- Active rheumatoid arthritis
- Polyarthritic form of severe, active juvenile idiopathic arthritis
- Moderate-to-severe psoriasis
- Severe psoriatic arthritis
- Mild-to-moderate Crohn's disease

The 3 major differences between metoject®/metex® PEN and a pre-filled syringe:

1 metoject®/metex® PEN is an autoinjector

By design, autoinjectors are easy to use as a major part of the injection process runs automatically. The injectors were initially designed to overcome the hesitation associated with self-administration of the conventional needle-based drug delivery device.

2 metoject®/metex® PEN has a different application process

The single steps that are required by the patient or health care staff in order to deliver the drug are different between PEN and a prefilled syringe. Please refer to page 14 for a detailed description of the process.

3 metoject®/metex® PEN is equipped with an automatic needle protection shield

After the injection is finished an automatic needle shield will slide over the needle and lock in place.

Autoinjector

Benefits of the metoject®/metex® PEN's device

Using the metoject®/metex® PEN's device offers advantages compared to a conventional syringe.

▶ Safety for patient and HCP after injection

metoject®/metex® PEN is additionally equipped with an automatic needle shield. After the injection with metoject®/metex® PEN is finished the automatic needle protection shield will move over the needle and irreversibly lock in place.

Needlestick prevention

metoject®/metex® PEN fulfills the requirements of EU directive 2010/32/EU implementing the framework agreement on prevention from sharp injuries in the hospital and healthcare sector.

The EU directive aims at employees of the hospital and healthcare sector to prevent injuries caused by medical sharps (including needle-sticks).

Color-coding of metoject®/metex® PEN

metoject®/metex® PEN offers the same spectrum of doses and color codes as the metoject®/metex® prefilled syringes.

Each dose has its unique color code facilitating an easy identification:

7.5 mg	10 mg	12.5 mg	15 mg	17.5 mg
20 mg	22.5 mg	25 mg	27.5 mg	30 mg

The color code is imprinted on the label which is attached to the PEN and on the outer package.

Not all doses may be marketed in your country

Available pack sizes and doses

Pre-filled autoinjectors containing

7.5 mg (0.15 ml)
10 mg (0.20 ml)
12.5 mg (0.25 ml)
15 mg (0.30 ml)
17.5 mg (0.35 ml)
20 mg (0.40 ml)
22.5 mg (0.45 ml)
25 mg (0.50 ml)
27.5 mg (0.55 ml)
30 mg (0.60 ml)

Solution are available in packs of

1, 4, 6 and 12 autoinjectors.

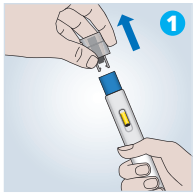
Not all doses and pack sizes may be marketed in your country.

Handling

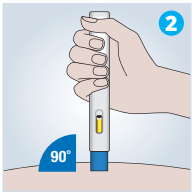
Application process

The metoject®/metex® PEN should be checked before injection. The medicine, that can be seen through the inspection window, should be yellow to brown in color and should not have any lumps or particles in it.

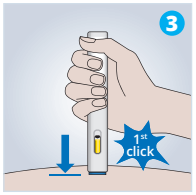
These are the five key steps of the metoject®/metex® PEN application process:



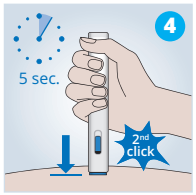
Removing the cap



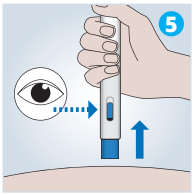
Positioning the pen



Pushing down the pen to start the injection



Holding pen in place to complete the injection



Finishing the injection

Recommended injection sites are the thigh and the lower part of the abdomen. If a caregiver administers the injection, the person may also use the area at the back of the upper arm. Each week a different injection site should be chosen to prevent possible skin reactions. The region 5cm around the belly button should be left out.

To prevent problems with the injection process we recommend to put special attention on the following points:

After the injection has started, the pen should be firmly pushed oh the skin for at least 5 seconds. A second click can be heard once the injection is finished. Otherwise the injection process cannot finish properly.

For injection video:

Scan QR code or visit www.metoject.com

Handling

Air bubble

Please note that there should be an air bubble in the syringe. This is to ensure all the liquid is pushed out of the syringe during injection. The air bubble is completely harmless.

Disposal

metoject®/metex® PEN is a single use autoinjector and cannot be refilled. After use, the pen should be disposed of in accordance with the local requirements. All other waste can be disposed of in the normal household waste.

Storage

metoject®/metex® PEN should be stored protected from light within the outer carton at a temperature below 25°C. If temperature rise above 25°C, please store the PEN in the fridge (above 0°C). Freezing should be avoided. Allow it to warm up before use. The shelf life of metoject®/metex® PEN is 30 months.

Travelling with metoject®/metex® PEN

Your patient should keep metoject®/metex® PEN in the closed original packaging and carry it in his/her hand luggage.

This prevents metoject®/metex® PEN from getting lost and the storage temperature of below 25 °C can be controlled. Should the temperature rise above 25 °C in the aircraft cabin, your patient should ask a stewardess to put metoject®/metex® PEN in a fridge on board.

If your patient plans to travel to warmer areas, he/she should consider to carry a small cooling box for the transport from the airport to the hotel. For the case of unexpected elongation of the journey, your patient should consider to take additional metoject®/metex® PEN with him/her.

Should your patient require any document to attest that he/she needs metoject®/metex® PEN for therapy when entering a foreign country, a certificate in English, Spanish, French, German and Turkish can be downloaded from our website (www.metoject.com). A completely filled out form should be accepted in most countries.

Methotrexate

Introduction methotrexate

Methotrexate (MTX) is the medicine most commonly used worldwide as systemic treatment for psoriasis[1] and psoriatic arthritis[2]. It has been in use for over 40 years.

Dosage and pharmaceutical forms

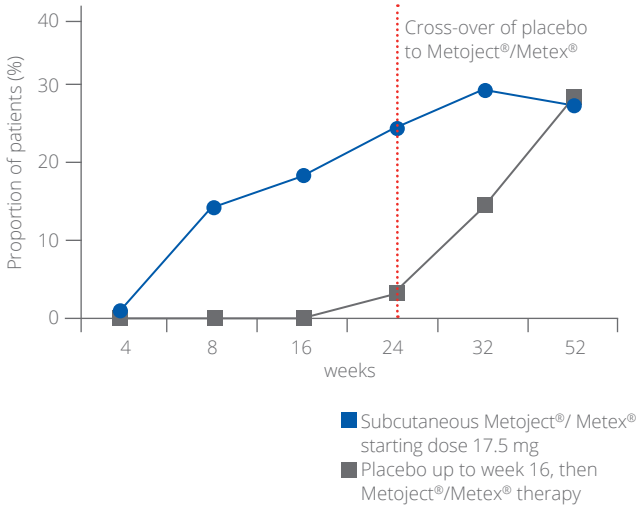
Patients with psoriasis or psoriatic arthritis are given a very small dose of methotrexate once a week, usually in the evening. The normal dose is between 7.5 and 25 mg per week.[3]

Methotrexate can be taken in the form of tablets (orally) or can be injected into the muscles (intramuscularly), into a vein (intravenously) or under the skin (subcutaneously), e.g. autoinjector.

Efficacy: What to expect

Response to treatment can generally be expected after 2–6 weeks.[3] Under therapy of metoject®/metex®, 51% of patients reach PASI75 by week 24 (see also figure on PASI90 score).[4] If the PASI score has not proved sufficiently effective after 8 weeks, an increase in the dose can be considered.[4]

PASI 90



Methotrexate

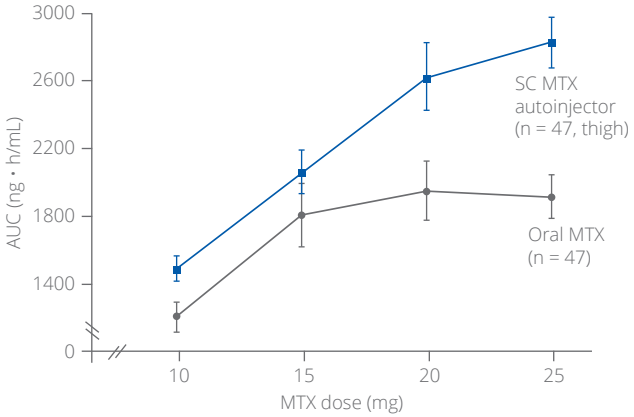
Bioavailability is higher with subcutaneous MTX

Following oral administration, methotrexate is absorbed from the gastrointestinal tract. In case of low-dosed administration (dos-ages between 7.5 mg/m² and 80 mg/m² body surface area), the mean bioavailability is approx. 70 %, but considerable inter-individual and intra-individual deviations are possible (25 – 100%). Bioavailability of subcutaneous MTX is nearly 100%.

Administration of methotrexate with the metoject®/metex® PEN resulted in a higher relative bioavailability compared to oral administration of MTX.[5]

Dose-proportional increase with injection

The systemic exposure of oral MTX plateaus at doses > 15 mg/week whereas with subcutaneous MTX the exposure increased in a dose-proportional manner.[6]

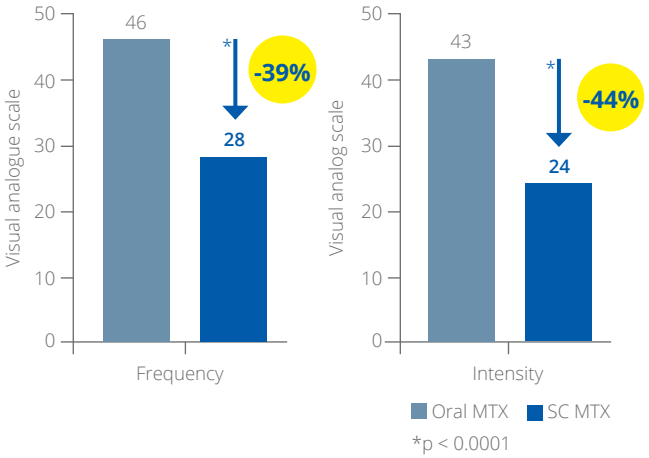


Methotrexate

Less gastrointestinal side effects

Also, nausea, vomiting, diarrhea, and abdominal pain have been shown to be significantly less frequent and intense with subcutaneous methotrexate than the oral form.[7,8]

Nausea



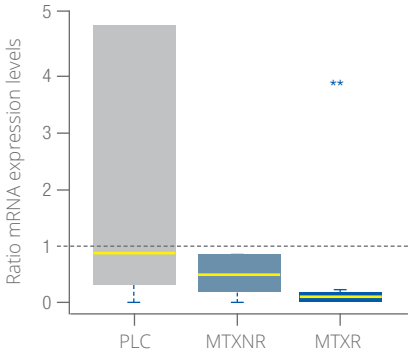
Extend therapy with subcutaneous methotrexate

A switch from oral to subcutaneous MTX prolonged mean drug survival - up to nearly 2 extra years.[9]

Immunomodulatory effects of metoject®/metex® in psoriasis therapy

Clinical response of subcutaneous metoject®/metex® involves inhibitory effects on Th1/Th17-mediated inflammation, e.g. the reduction of cytokine mRNA of INF-γ and IL-17α (see figure below). Also, $CD11c^+$ dentritic cells were reduced and $CD3^+$ T cells were almost back to normal level at week 16.[10] Pairs of biopsies were taken from psoriatic skin of 27 patients at baseline and week 16 during the 52-week, multicentre, double-blind, placebo-controlled phase-III trial METOP.[4]

IL-17α



Cutaneous mRNA expression levels of IL-17α and IFN-α in quantitative real-time PCR analyses as x-fold change of week-16 compared to baseline values: Values above 1 (dashed line) indicate –fold increase and below 1 indicate –fold decrease. **p<0.001. Box-and-whisker plots with median.

PLC=placebo
MTXNR=MTX non-responder,
MTXR=MTX responder

Safety

Considerations before prescribing metoject®/ metex® PEN

Patients must be clearly informed that the therapy has to be applied only once a week, not every day. Discuss with your patient the most suitable day of the week.

How metoject®/metex® PEN affects fertility, pregnancy and lactation

Woman of childbearing potential/Contraception in females

Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter. Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.[3]

Contraception in males

It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure. As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 3 months after cessation of methotrexate. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.[3]

Fertility

Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, and to cause impaired fertility, affecting spermatogenesis and oogenesis during the period of its administration. The effects appear to be reversible after discontinuing therapy in most cases.[3]

Safety

Pregnancy

Methotrexate is contraindicated during pregnancy in non-oncological indications. If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.[3]

In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester. Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related). Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.[3]

- Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
- Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected.

When methotrexate was discontinued prior to conception, normal pregnancies have been reported.[3]

Breast feeding

Methotrexate is excreted in human milk. Because of the potential for serious adverse reactions in breastfed infants, Methotrexate is contraindicated during breast-feeding. Therefore breastfeeding must be discontinued prior and during administration.[3]

Undesirable effects

It is indispensable that patients undergoing therapy are subjected to the appropriate pre-treatment examinations as well as constant monitoring so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay (please see Monitoring planner, page 30-32).[3]

The following list shows the most common undesirable effects (frequency of > 1%)*:

- **Blood and lymphatic system disorders**
  Leukopenia, anaemia, thrombopenia.
- **Nervous system disorders**
  Headache, tiredness, drowsiness.

Safety

- **Respiratory, thoracic and mediastinal disorders**
  Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia.
- **Gastrointestinal disorders**
  Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain, oral ulcers, diarrhoea.
- **Hepatobiliary disorders**
  Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin).
- **Skin and subcutaneous tissue disorders**
  Exanthema, erythema, pruritus.

PLEASE NOTE:

All severe psoriasis patients should be screened for severe liver fibrosis irrespective of their systemic medication.

Approximately every 7th patient of a UK cohort was suffering from advanced liver fibrosis.

Most patients were not taking MTX and would not have identified using current guidelines.[11]

**Please refer to the SPC for the full list of undesirable effects*

Contraindications

metoject®/metex® PEN is contraindicated in the case of

- Hypersensitivity to the active substance or to any of the excipients
- Severe liver impairment
- Alcohol abuse
- Severe renal impairment (creatinine clearance less than 30 ml/min.)
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- Serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes
- Ulcers of the oral cavity and known active gastrointestinal ulcer disease
- Pregnancy, breast-feeding
- Concurrent vaccination with live vaccines

How to minimize side effects

Taking folic acid helps to reduce potencial side effects of the methotrexate and is recommended in the European guidelines, e.g., 5 mg of folic acid once weekly 24 hours after methotrexate application.[12] The American guidelines recommend 1–5 mg daily except on the day of methotrexate intake.[13]

Safety

Taking the medicine after the evening meal helps to manage nausea and to sleep over any fatigue.[14]

Choosing the week day of methotrexate injection according to the life style of the patient may help to lower the impact of any side effect.[14]

Patient behaviour

Getting vaccinations: Patients should stay away from infected people e.g. with chickenpox. Also, patients should get vaccinated — except with live vaccines such as yellow fever, MMR and rubella.

Drinking alcohol: Patients under methotrexate therapy are asked to keep their alcohol intake low. A recent publication concluded that alcohol consumption of less than 14 units per week, e.g. 6 pints of 4% beer, or 6 glasses of 13% wine (175 ml) does not appear to be associated with an increased risk of transaminitis.[15]

Stop smoking and avoid obesity: Besides alcohol consumption, smoking and obesity have been closely correlated to more severe psoriasis symptoms. Dermatologists should counsel and support patients on lifestyle modifications.[16]

Monitoring planner[3, 12, 17, 18]

Laboratory and clinical parameters[3,12,17,18]

Parameter	Pre-treatment	First month, 1–2 x weekly[3]	Second to sixth months, 1 x monthly[3]	From seventh month, once quarterly[3]
Complete blood count*	x	x[§]	x[§]	x
Liver enyzmes**	x	x[§]	x[§]	x
Kidney function: Serum creatinine	x	x[§]	x[§]	x
Urine status	x	x[3,18]	x[3,18,§]	x[3,18,§]
Pregnancy test	x			
Chest X-ray	x			
HBV/HCV	x			
HIV	x			
Serum albumin***	x	x[§]	x[§]	x
PIIINP where available****	x		Every 3 months[12,17,18]	

Further recommended examinations include assessment of the gastrointestinal and respiratory system, examination for mucosal changes of the mouth and throat and exclusion of inactive, chronic infections and fever.[3] Weekly folate (5 mg, 24 h after MTX)[17] is recommended.[18]

[§]Please note that, according to the underlying recommendations, there may be deviations with regard to the period for repeating the measurement. *Hb, Hct, erythrocytes, leukocytes, differential blood count, platelets **ALT, AST, AP, GGT, albumin, bilirubin, LDH[2] ***In selected cases (e.g. suspected hypoalbuminaemia or administration of drugs with a high binding affinity for serum albumin) ****In case of abnormal PIIINP during MTX treatment a hepatologist should be consulted.

Interpretation of laboratory and clinical diagnostics

Parameter	Laboratory value	Recommended action
Blood count:		Contraindications: pre-existing blood dyscrasias such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia[3]
Leukocytes	<3.0 x 10^9/l	Decrease dose or discontinue medication[18]
Neutrophils	<1.0 x 10^9/l	Decrease dose or discontinue medication[18]
Platelets	<100 x 10^9/l	Decrease dose or discontinue medication[18]

Note: Country-specific recommendations may differ in monitoring intervals
**Liver biopsy when necessary in selected cases*

MCV	>105 fl	Withhold and check serum B12, folate and thyroid function tests and discuss with specialist if necessary[18]
Liver enzymes		Contraindication: severe liver impairment[3]
AST, ALT	<2 times baseline value >2-3 times baseline value	Repetition of liver function tests[18] Withhold/decrease dose, consider discussion with gastroenterologist[18]
Bilirubin	>5 mg/dl (85.5 µmol/l)	Contraindicated[3]
Creatine clearence	30–59 ml/min <30 ml/min	Reduce dose by 50%[3] Contraindicated, discontinue medication[3]
Chest X-ray	Infiltrate	With fever, cough, dyspnoea, hypoxemia there is suspicion of pneumonitis; exclude infection; discontinue medication[3]
PIIINP	(i) > 8 mg/l on two occasions (ii) > 4.2 mg/l in a 12 month period (iii) > 10 mg/l on one occasion	Refer to specialist[18]
Serum albumin	Unexplaind drop	Discuss with specialist

[1] Gyulai R, Bagot M, Griffiths CEM et al. J Eur Acad Dermatol Venereol 2015; 29: d277–94. https://doi.org/10.1111/jdv.12495
[2] Gossec L, Kerschbaumer A, Ferreira RJO et al. Ann Rheum Dis. 2024; 83(6): 706-719.
[3] 3 Summaries of product characteristic (SPC) for Metoject 50 mg/ml solution for injection (common version: 08/2024).
[4] Warren RB, Mrowietz U, von Kiedrowski R et al. Lancet 2017; 389: 528–37.
[5] Pichlmeier U, Heuer KU Clin Exp Rheumatol 2014; 32: 563–571. PMID: 24983446
[6] Schiff MH, Jaffe JS, Freundlich B Ann Rheum Dis 2014; 73: 1549–1551
[7] Rutkowska-Sak L, Rell-Bakalarska M, Lisowska B. Reumatologia 2009; 47: 207-211
[8] Fraes Diernæs JE, Kromann CB, Boel M et al. J Am Acad Dermatol. 2022;87(4): 920-922.
[9] Hollywood A, O'Keeffe C, Boggs, J et al. Br J Dermatol. 2020; 182(5): 1290–1.
[10] Reich K, Reich JLK, Falk TM et al. Br J Dermatol. 2019; 181(4): 859-862.
[11] Maybury CM, Porter HF, Kloczko E et al. JAMA Dermatol. 2019; 155(9): 1028-1032.
[12] Nast A, Smith C, Spuls PI et al. J Eur Acad Dermatol Venereol. 2020; 34(11): 2461-2498.
[13] Menter A, Korman NJ, Elmets CA et al. JAAD 2009; 61: 451–85.
[14] Royal College of Nursing, Administering Subcutaneous Methotrexate for Inflammatory Arthritis. 2021, Publication code: 009675.
[15] Humphreys JH, Warner A, Costello R, et al. Ann Rheum Dis 2017; 76:1509 – 14.
[16] Lebwohl M. Ann Internal Med 2018; 168: ITC49-64. doi: 10.7326/AITC201804030
[17] Nast A, Altenburg A, Augustin M et al. J Dtsch Dermatol Ges. 2021; 19(6): 934-150.
[18] Warren RB, Weatherhead SC, Smith CH et al. Br J Dermatol 2016; 175: 23-44.

Metoject® PEN / metex® Pen 7.5 mg / 10 mg / 12.5 mg / 15 mg / 17.5 mg / 20 mg / 22.5 mg/ 25 mg/ 27.5 mg / 30 mg solution for injection in pre-filled pen

Qualitative and quantitative composition: 1 pre-filled pen with 0.15 ml (0.20 ml; 0.25 ml; 0.30 ml; 0.35 ml; 0.40 ml; 0.45 ml; 0.50 ml; 0.55 ml; 0.60 ml) contains 7.5 mg (10 mg; 12.5 mg; 15 mg; 17.5 mg; 20 mg; 22.5 mg; 25 mg; 27.5 mg; 30 mg) methotrexate. *Excipients:* NaCl, NaOH, HCl, water for injections. **Therapeutic indications:** Active rheumatoid arthritis in adult patients; polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate; moderate to severe psoriasis in adult patients who are candidates for systemic therapy, and severe psoriatic arthritis in adults; mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines. **Posology and method of administration:** Should only be prescribed by physicians who are familiar with the various characteristics of the medicinal product and its mode of action. Patients must be educated to use the proper injection technique. The first injection of Metoject PEN should be performed under direct medical supervision. A*dults, rheumatoid arthritis:* The recommended initial dose is 7.5 mg of Metoject once weekly, administered subcutaneously. Depending on the individual activity of the disease and tolerability, the dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should in general not be exceeded. *Polyarthritic forms of juvenile idiopathic arthritis:* The recommended dose is 10-15 mg/m^2 body surface area (BSA)/once weekly, administered subcutaneously. In therapy-refractory cases the weekly dosage may be increased up to 20 mg/m^2 BSA/once weekly. Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population. *Psoriasis vulgaris, psoriatic arthritis:* Test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. *Crohn's disease:* Induction treatment: 25 mg/week administered subcutaneously. Response to treatment can be expected after approximately 8 -12 weeks. Maintenance treatment: 15 mg/week. *Elderly:* Dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves. If changing the oral to parenteral administration a reduction of dose may be required due to the variable bioavailability. **Contraindications:** Hypersensitivity to methotrexate or any of the excipients; severe liver impairment; alcohol abuse; severe renal impairment (creatinine clearance < 30 ml/min); pre-existing blood dyscrasias (bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anaemia); serious, acute or chronic infections such as tuberculosis, HIV, other immunodeficiency syndromes; ulcers of the oral cavity and known active gastrointestinal ulcer disease; pregnancy, breastfeeding; concurrent vaccination with live vaccines. **Special warnings and precautions for use:** In the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease, Metoject PEN (methotrexate) must only be used once a week. Dosage errors in the use can result in serious adverse reactions, including death. **Undesirable effects:** Most serious adverse reactions of methotrexate include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome. Most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite and abnormal liver function tests e.g. increased ALAT, ASAT, bilirubin, alkaline phosphatase. Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus. *Effects:* Pharyngitis, infection (incl. reactivation of inactive chronic infection), sepsis, conjunctivitis. Lymphoma. Leukopenia, anaemia, thrombopenia, pancytopenia, agranulocytosis, severe courses of bone marrow depression, lymphoproliferative disorders, eosinophilia. Allergic reactions, anaphylactic shock, hypogammaglobulinaemia. Precipitation of diabetes mellitus. Depression, confusion, mood alterations. Headache, tiredness, drowsiness, dizziness, pain, muscular asthenia or paraesthesia/ hypoaesthesia, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis, encephalopathy/ leukoencephalopathy. Visual disturbances, impaired vision, retinopathy. Pericarditis, pericardial effusion, pericardial tamponade. Hypotension, thromboembolic events. Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever, pulmonary fibrosis, Pneumocystis jirovecii pneumonia, shortness of breath and bronchial asthma, pleural effusion, epistaxis, pulmonary alveolar haemorrhage. Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain, oral ulcers, diarrhoea, gastrointestinal ulcers and bleeding, enteritis, vomiting, pancreatitis, gingivitis, haematemesis, haematorrhea, toxic megacolon. Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin), cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin, acute hepatitis, hepatic failure. Exanthema, erythema, pruritus, photosensitivity reactions, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticarial, increased pigmentation, acne, petechiae, ecchymosis, allergic vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia, skin exfoliation/ dermatitis exfoliative. Arthralgia, myalgia, osteoporosis, stress fracture, osteonecrosis of jaw (secondary to lymphoproliferative disorders). Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition, renal failure, oliguria, anuria, electrolyte disturbances, proteinuria. Inflammation and ulceration of the vagina, loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge. Fever, wound-healing impairment, asthenia, injection site necrosis, oedema. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed, decreasing during therapy. **Overdose:** Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate. **Legal classification:** POM **Marketing authorisation holder:** medac medac GmbH, Theaterstr. 6, 22880 Wedel, Germany. **Date of revision of text:** 18.09.2024 **Registered in the following countries:** Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, United Kingdom

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