Package leaflet: Information for the user
Methotrexate 2.5 mg tablets
methotrexate

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 or pharmacist.
- 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 Methotrexate Tablets are and what they are used for
2. What you need to know before you take Methotrexate Tablets
3. How to take Methotrexate Tablets
4. Possible side effects
5. How to store Methotrexate Tablets
6. Contents of the pack and other information

1. What Methotrexate Tablets are and what they are used for

Methotrexate Tablets contain the active ingredient methotrexate. Methotrexate is an antimetabolite and immunosuppressant (medicine which affects the reproduction of the body's cells and reduces the activity of the immune system).

Methotrexate is used to treat:
- active rheumatoid arthritis in adult patients,
- severe resistant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids,
- severe psoriatic arthritis in adult patients.

Your doctor will be able to explain how Methotrexate Tablets might help in your particular condition.

2. What you need to know before you take Methotrexate Tablets

Do not take Methotrexate Tablets:
- if you are allergic to methotrexate, or any of the other ingredients of this medicine (listed in section 6);
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility");
- if you have significant liver disease (your doctor decides the severity of your disease);
- if you have significant kidney disease (your doctor decides the severity of your disease);
- if you have or have had a bone marrow disease or serious blood disorders;
- if your alcohol consumption is high
- If you have an impaired immune system
- if you have severe acute or existing infections e.g tuberculosis or HIV
- if you have inflammation or ulcers in your mouth
- if you have active phase gastrointestinal ulcers (e.g. peptic ulcer or ulcerative colitis)
- During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.

Warnings and precautions

Important warning about the dose of Methotrexate tablets (methotrexate):

Take Methotrexate tablets (methotrexate) **only once a week** for the treatment of rheumatic or skin disease.

Taking too much of Methotrexate tablets (methotrexate) may be fatal.

Please read section 3 of this leaflet very carefully.

If you have any questions, please talk to your doctor or pharmacist before you take this medicine.

Talk to your doctor, pharmacist or nurse before taking Methotrexate Tablets if you suffer from or have suffered in the past from any of the following conditions;
- have or have had any liver or kidney disease;
- are using any other medicines or vitamin products (see section "Other medicines and Methotrexate Tablets");
- have ulcerations in your stomach or bowel (peptic ulcer or ulcerative colitis);
- are in poor general condition;
- have received any vaccinations recently or are you due to have any;
- have any inactive, prolonged infections (e.g. tuberculosis, hepatitis B or C, shingles [herpes zoster]) ;
- Diabetes mellitus treated with insulin.
- You have problems with lung function
- You are severely overweight
- You have abnormal accumulation of liquid in the abdomen or in the cavity between the lungs and chest wall (ascites, pleural effusions)
- You are dehydrated or suffer from conditions leading to dehydration (e.g. dehydration as a result of vomiting, diarrhoea or inflammation of the mouth and lips).

Acute bleeding from the lungs in patients with underlying rheumatologic disease has been reported with methotrexate. If you experience symptoms of spitting or coughing up blood you should contact your doctor immediately.

If you have experienced problems with your skin after radiation therapy (radiation induced dermatitis) or sun-burn, these conditions can reappear when taking methotrexate.

Diarrhoea can be a possible side effect of Methotrexate and requires an interruption of therapy. If you suffer from diarrhoea please speak to your doctor.

Special precautionary measures for treatment with Methotrexate tablets

Methotrexate temporarily affects sperm and egg production, which is reversible in most cases. Methotrexate can cause miscarriage and severe birth defects. You must avoid becoming pregnant when using methotrexate and for at least six months after treatment has stopped. See also section "Pregnancy, breast-feeding and fertility".

Skin changes caused by psoriasis can worsen during treatment with methotrexate if exposed to ultraviolet irradiation

Before the start of treatment and recommended follow-up examinations and precautions

Before treatment is started your doctor may carry out blood tests, and also to check how well your kidneys and liver are working. You may also have a chest X-ray. Further tests may also be done during and after treatment. Do not miss appointments for blood tests.

If the results of any of these tests are abnormal, treatment will only be resumed when all readings are back to normal.

Even when methotrexate is used at low doses, serious side effects can occur. Your doctor will carry out blood and urine tests to make sure that any side effects are identified quickly.

Brain disease (encephalopathy/leukoencephalopathy) has been reported as a side effect in patients receiving methotrexate for treating cancer; it cannot be excluded that this may also happen when you take Methotrexate tablets for the treatment of rheumatoid arthritis or psoriasis.

Children and adolescents
Methotrexate tablets are not recommended in children and adolescents for rheumatoid arthritis and psoriasis.

Other medicines and Methotrexate Tablets
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription.

Other concomitant medication may affect the efficacy and safety of this medicine. Methotrexate Tablets may also affect the efficacy and safety of other medications.

Remember to tell your doctor about your treatment with Methotrexate Tablets, if you are prescribed another medicine while the treatment is still ongoing. It is especially important to tell your doctor if you are using:
- certain antibiotics (such as chloramphenicol, penicillins, glycopeptides, sulfonamides, ciprofloxacin, cefalotin, trimethoprim/sulfamethoxazole and tetracyclines);
- diuretics, triamterene (water tablets);
- medicines for lowering blood sugar levels such as metformin
- anticonvulsant medicines such as phenytoin or levetiracetam (medicine often used to treat epilepsy); a medicine that binds bile acid and can be used e.g. to lower cholesterol levels (cholestyramine)
- probenicid (medicine used to treat gout);
- folic acid (vitamin preparations);
- omeprazole or pantoprazole (medicine used to stop the production of stomach acid);
- agents that may be harmful to kidneys and liver [e.g. sulfasalazine and leflunomide (medicines for rheumatic disease), alcohol];
- anticancer agents (e.g. doxorubicin, cisplatin, mercaptopurine);
- medicines against pain and/or inflammation known non-steroidal anti-inflammatory medicines (e.g. diclofenac and ibuprofen, salicylates like acetylsalicylic acid (aspirin) and pyrazoles like metamizole)
- other treatments for rheumatoid arthritis or psoriasis such as azathioprine, leflunomide, sulphasalazine (a medicine that besides arthritis and psoriasis is also used to treat an ulcerative colitis), phenylbutazone, or amidopyrine
- theophylline (medicine used to treat respiratory diseases);
- cyclosporine (an agent that can suppress or prevent the immune response).
- barbiturates (sleeping injection)
- tranquillisers
- oral contraceptives
- retinoids (used to treat psoriasis and other skin disorders)
- pyrimethamine (which is used to prevent and treat malaria)
- any vaccination with a live vaccine (must be avoided), such as measles, mumps, influenza or yellow fever vaccines.

Tell your physician about use of Methotrexate Tablets during your next visits.

Methotrexate Tablets with food, drink and alcohol
Alcohol should be avoided during methotrexate therapy and you should avoid excessive consumption of coffee, soft drinks containing caffeine and black tea as this may enhance side effects or interfere with the efficacy of methotrexate. Also, make sure you drink plenty of liquids during treatment with methotrexate because dehydration (reduction in body water) can increase the toxicity of methotrexate.

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

Pregnancy
Do not use Methotrexate tablets during pregnancy or if you are trying to become pregnant. Methotrexate can cause birth defects, harm the unborn child or cause miscarriage. It is associated with malformations of the skull, face, heart and blood vessels, brain and limbs. Therefore, it is very important that Methotrexate is not given to pregnant patients or patients planning to become pregnant. In women of child-bearing age any possibility of pregnancy must be excluded with appropriate measures, e.g. a pregnancy test before starting treatment. You must avoid becoming pregnant whilst taking methotrexate and for at least 6 months after treatment is stopped by using reliable contraception throughout this time (see section "Warnings and precautions").

If you do become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. You should be offered advice regarding the risk of harmful effects on the child through treatment.

If you wish to become pregnant you should consult your doctor, who may refer you for specialist advice before the planned start of treatment.

Breast-feeding
Do not breastfeed during treatment, because methotrexate passes into breast milk. If your attending doctor considers treatment with methotrexate absolutely necessary during the lactation period, you must stop breast-feeding.

Fertility

Male fertility
The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes methotrexate less than 30 mg/week. However, a risk cannot be completely excluded. Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm production with the potential to cause birth defects. Therefore, you should avoid fathering a child or to donate semen whilst taking methotrexate and for at least **6** months after treatment is stopped.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You can feel fatigue and dizziness during Methotrexate Tablets treatment. Do not drive or use machines if you have such symptoms.

Methotrexate Tablet contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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

3. How to take Methotrexate Tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
- Take Methotrexate Tablets once a week.
- Patients with rheumatoid arthritis, psoriatic arthritis or psoriasis will usually take their tablets orally **once a week** on the same day each week.
- Do not take tablets more often than your doctor has told you to.
- **Daily administration can lead to serious toxic effects, including death.**
- Take the tablets with a glass of water whilst sitting upright or standing.

Recommended dose is
Rheumatoid arthritis
The recommended dose is 7.5 mg - 15 mg **orally, once weekly**.

Psoriasis
The recommended dose is 7.5 mg - 15 mg **orally, once weekly**.

Take Methotrexate Tablets only once a week

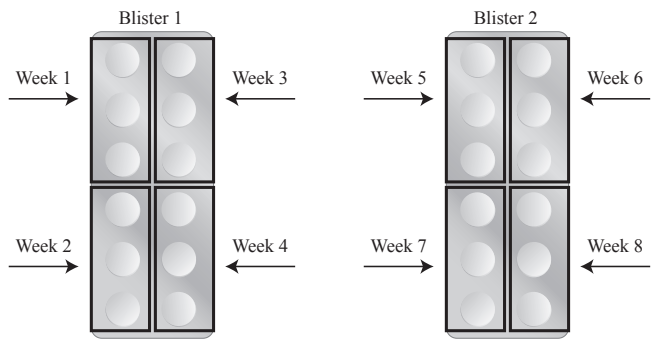
Graphic illustration on the taking of tablets in rheumatic or skin disease for adults

Each package of Methotrexate 2.5 mg tablets contains 24 tablets. Each tablet contains a dose of 2.5 mg methotrexate. Below are diagrams of the recommended amount of tablets to be taken for each of the inflammatory indications described above. These diagrams are an example- your doctor may change your dose, if required. It is very important that you take the correct number of tablets prescribed by your doctor. Remember also that the dose prescribed by your doctor must be done once a week.

This medicine should NOT BE TAKEN EVERY DAY for the treatment of rheumatoid arthritis and psoriasis

Rheumatoid arthritis and psoriasis
The initial dose in adults is 3 tablets (7.5 mg) **once a week**. Therefore, the container of Methotrexate 2.5 mg tablets containing 24 tablets covers treatment for 8 weeks, the distribution is given as below:

Initial dosage: 3 X 2.5 mg tablets per week (7.5 mg per week)



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Patient card

THIS PATIENT CARD IS ONLY INTENDED FOR PATIENTS WHO USE A METHOTREXATE-CONTAINING MEDICINE FOR ARTHRITIS AND PSORIASIS.

IF YOU USE METHOTREXATE FOR ONE OF THE ABOVE MENTIONED INDICATIONS, YOU SHOULD ONLY TAKE METHOTREXATE ONCE A WEEK

Write here in full the day of the week for intake: _____

Do not take more than the prescribed dose.

Overdose could lead to serious adverse effects and may be fatal. Symptoms of overdose are e.g. sore throat, fever, mouth ulcers, diarrhoea,

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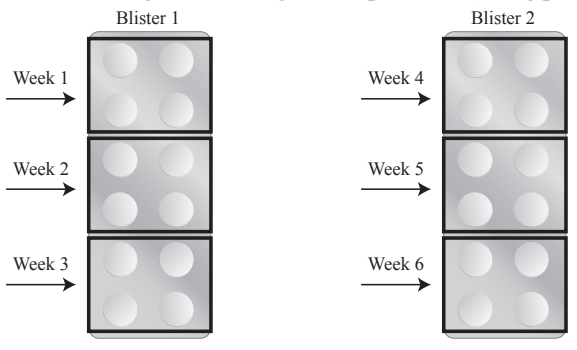
Date: 13/04/2020 UK

Patient card text addition

Increased dosage: 4 X 2.5 mg tablets per week (10 mg per week)



This should be adjusted according to your response to treatment and side effects.

Proper procedures for safe handling of cytotoxic agents should be administered. Anyone handling methotrexate should wash their hands after administering a dose. Disposable gloves should be used when handling methotrexate tablets. Women who are pregnant, planning to be or breast-feeding should not handle methotrexate.

Use in children
Not recommended for use in children.

If you take more Methotrexate Tablets than you should
If you take (or someone else has taken) more of the medicine than you should, a physician or nearest hospital casualty department must be contacted immediately.

An overdose of methotrexate can lead to severe toxic reactions, including death. Overdose symptoms may include easy bruising or bleeding, unusual weakness, mouth sores, nausea, vomiting, black or bloody stools, coughing up blood or vomit that looks like coffee grounds, and decreased urinating. See section 4.

Take your medicine package with you if you go to a doctor or hospital.

If you forget to take Methotrexate Tablets
If you forget to take a dose, take it as soon as you remember if this is within two days. However, if you have missed a dose by more than two days, please contact your doctor for advice. **Do not take a double dose to make up a forgotten dose.**

Make sure before your holiday or trip that you have enough of your medicine.

If you stop taking Methotrexate Tablets
Do not stop taking Methotrexate Tablets unless your doctor tells you to. Should you need to stop taking Methotrexate Tablets, your doctor will have decided which is the best method for you.

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

4. Possible side effects

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

In general, the incidence and severity of adverse reactions of methotrexate are related to dose and frequency of administration. Most adverse reactions are reversible if detected early.

Serious side effects
Contact your doctor or hospital emergency department immediately if you have any of the following symptoms:

Uncommon (may affect up to 1 in 100 people)
- A cough producing a thick mucus, difficulty breathing, fever or shortness of breath. You may be suffering from pneumonitis, pulmonary fibrosis or pneumonia.
- Tightness in your chest, difficulty breathing, swelling of the face, throat or hands, feeling dizzy or faint. These could be signs of a severe allergic reaction.
- Severe skin reactions, including peeling and blistering of the skin, mouth, eyes and genitals and numerous pus filled spots with a fever. You could be suffering from Stevens-Johnson syndrome or toxic epidermal necrolysis.
- Fever and deterioration of your general condition, or fever with local infections such as in the throat or mouth. You may have a reduced number of white blood cells (possibly due to bone marrow depression) and your resistance to infection may be decreased.
- pain or difficulties in passing urine
- You may be suffering from kidney damage

Rare (may affect up to 1 in 1,000 people)
- Loss of appetite, nausea, itchy skin, yellowing of the skin or eyes, fever, swollen or tender stomach. You may be suffering from inflammation or damage of the liver.
- Vomiting blood, passing black tar-like stools and pain in the stomach. You may have a stomach ulcer or bleeding.
- Cramping pain, heavy ache or swelling in the leg, redness, breathlessness, chest pain or sudden collapse. You may have a blood clot.
- reduction or lack of urine production
- A high temperature, chills and shivering, a fast heartbeat, rapid breathing, confusion or dizziness. You may have sepsis as the result of an infection

Very rare (may affect up to 1 in 10,000 people)
- Blood in the urine,
- Difficulty of speaking or communicating
- Convulsions

Not known (frequency cannot be estimated from the available data)
- spitting or coughing blood
- certain brain disorders (encephalopathy/leucoencephalopathy)

Other side effects

Very common side effects (may affect more than 1 in 10 people)
- inflammation of throat or sore mouth and lips,
- dyspepsia,
- loss of appetite,
- nausea,
- vomiting,
- stomach pain,
- an increase in liver enzymes.

Common (may affect up to 1 in 10 people)
- infection,
- diarrhoea
- exhaustion
- tiredness,
- headache,
- dizziness,
- rash or large red spots on the skin,
- hair loss,
- drowsiness
- exanthema
- mouth ulcers

Uncommon (may affect up to 1 in 100 people)
- reduced blood clotting,
- change to your blood count,
- anaemia,
- itching,
- swelling of the lymph nodesmay be a sign of a cancer of the lymphatic system (lymphoma),
- vaginal inflammation and ulcers.
- vertigo
- fatty liver
- decrease in serum albumin levels
- herpes-like eruptions of the skin,
- increased pigmentation of skin
- osteoporosis
- pain in joints or muscles,
- appearance of local tissue lumps
- ulcers of the bladder
- chills

Rare (may affect up to 1 in 1,000 people)
- depression,
- confusion,
- hemiparesis (weakness on one side of the body),
- diabetes,
- low blood pressure (hypotension),
- shortness of breath,
- inflamed gums,
- sore throat,
- acne,
- whitening of the skin,
- raised itchy rash,
- sensitivity to light,
- burning in psoriatic lesions on the skin,
- skin ulcers,
- shingles or painful skin rash,
- menstrual disorders,
- impotence,
- reduced sex drive.
- A blood disorder characterised by the appearance of very large red blood cells (megaloblastic anaemia),
- mood fluctuations
- inflammation of the heart sac, accumulation of fluid in the heart sac,
- inflammation of the small intestine
- bloody stools
- detachment of the nail,
- darkened areas on the nails
- red or purple spots due to bleeding from blood vessels
- allergic inflammation of blood vessels
- skin lesions resembling sunburn or dermatitis after radiotherapy
- stress bone fracture
- abnormal levels of electrolytes in blood
- physical weakness
- Fever
- slow wound healing
- stopping breathing

Very rare (may affect up to 1 in 10,000 people)
- immune deficiency (hypogammaglobulinaemia),
- irritation,
- sleepiness, tiredness (lethargy),
- visual disturbance,
- redness and irritation of the thin membrane that covers the eye (conjunctivitis),
- fluid or swelling around the heart or lungs,
- inflammation of blood vessels, often with skin rash (vasculitis),
- infection of lungs,
- dry cough,
- vomiting of blood,
- boils,
- blood like bruises or small blood vessels on the surface of the skin,
- fertility problems,
- low sperm count,
- infertility,
- vaginal bleeding or discharge,
- enlargement of male breast tissue.
- lymphoproliferative disorders (excessive growth of white blood cells)
- Serious disorders of bone marrow
- increased susceptibility to infections
- insomnia
- psychoses,
- reduced levels of antibodies
- mild temporary problems in intellectual functions (“brain fog”)
- having unusual sensations in the head
- brain swelling
- ringing in ears
- pain,
- muscle weakness,
- pins and needles,
- changes in sense of taste (metallic taste),
- inflammation of the lining of the brain,
- paralysis,
- inflammation of the linings around the lungs,
- liver failure,
- inflammation of blood vessels,
- chronic obstructive lung disease
- inflammation of sweat glands,
- fingernail infections

Not known (frequency cannot be estimated from the available data)
- abnormally low number of blood cells,
- sepsis resulting in death,
- miscarriage,
- foetal damages,
- increased risk of toxic reactions during radiotherapy,
- increase in the number of white blood cells and inflammation of the lung tissue.
- scaly, red skin patches associated with psoriasis may get worse when exposed to sources of ultraviolet light, such as the sun, and taking Methotrexate tablets.
- bleeding from the lungs
- bone damage in the jaw (secondary to excessive growth of white blood cells)
- reactivation of inactive chronic infection
- impaired vision
- damage to the retina of the eye
- enlargement of colon associated with inflammation/infection
- pancreatitis
- pathological change of the white matter of the brain (leukoencephalopathy)
- nosebleed,
- asthma,
- presence of protein in urine

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 Yellow Card Scheme at:www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Methotrexate Tablets

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

This medicinal product does not require any special temperature storage conditions.

Blister: Keep the blister in the outer carton in order to protect from light.

HDPE container: Store in original container in order to protect from light.

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

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

6. Contents of the pack and other information

What Methotrexate Tablet contains
- The active substance is methotrexate. Each tablet contains methotrexate 2.5 mg.
- The other ingredients are: anhydrous calcium hydrogen phosphate, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, talc, magnesium stearate.

What Methotrexate Tablets look like and contents of the pack

Methotrexate 2.5 mg tablets are yellow, circular, biconvex uncoated tablets with dimension of 4.50 mm ± 0.2 mm plain on both sides. Methotrexate 2.5 mg tablets are available in HDPE bottles containing 25 or 100 tablets and Blister pack containing 10, 24, 25, 28 30, 50 or 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Cipla (EU) Limited
Dixcart House, Addlestone Road,
Bourne Business Park,
Addlestone, Surrey, KT15 2LE,
United Kingdom

Manufacturer
Cipla (EU) Limited,
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Bourne Business Park,
Addlestone, Surrey, KT15 2LE,
United Kingdom

Cipla Europe NV,
De Keyserlei 58-60,
Box 19, 2018 Antwerp,
Belgium

S&D Pharma CZ
spol. s.r.o, Theodor 28
Pchery (Pharmos a.s. facility), 27308
Czech Republic.

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vomiting, skin rashes, bleeding or unusual weakness. If you think you have taken more than the prescribed dose, consult a physician immediately.

Always show this card to health care professionals not familiar with your methotrexate treatment to alert them about your once weekly use (e.g. on hospital admission, change of care).

For more information, please read the patient leaflet inserted in the package.

Date: 13/04/2020 UK

Patient card text addition

Font: Times New Roman (Regular) Times New Roman (Bold)
Body text : 9pt Sub Heading : 10pt Main Heading : 12pt Leading between two lines : 1pt

Proofless

UK

Patient card text addition

PACKAGING DEVELOPMENT

Product Name: Methotrexate 2.5mg Tablet Cipla (EU) Own Blister Pack-Container (Patient card text addition)	**Material No.:** 21082135	**Version:** 01	**Item:** Leaflet	**Co-ordinator:** Shweta	**Artist:** Avadhoot	**Date:** 13/04/2020
Colours: BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA) ■ Black				**INK:** Oil based Ink from DIC OR MICRO		
Design: Booklet	**Supersedes:** 21079883			**Software:** Illustrator CC		
Fonts: ------			**Links:** NA			
Actual Size: 200 x 670 mm	**Size after folding:** 25 x 50 mm	**2D Code:** 21082135	**Grain Direction :** Parallel to length			**Screen : # __**
Material: 40 GSM ITC Paper with plain perforated tape			**Varnish: --**	**Artwork Print Size:** ☐ actual ☐ scaled		
Path: Avadhoot \ F:\Export\EUROPE\DTM\Methotrexate\UK \ 21082135 Methotrexate 2.5mg Tablet Cipla (EU) Own Blister Pack-Container (Patient card text addition) PIL UK.ai						

- **Instructions / Remark: NA**
- Any deviation must be brought to the notice of packaging development co-ordinator immediately.
- For any clarification, please contact packaging development co-ordinator immediately.
  NO CHANGES IN ARTWORK SHOULD BE DONE BY THE PRINTER
- The printer should verify the e-proof against the approved artwork before submitting for approval and the e-proof should have printer details .

Checked by	Artist	Cordinator	file loaded in Server	Section Head
Pharma Code	☐	☐		
2D Code	☐	☐		
QR Code	☐	☐		
Bar Code	☐	☐		
Artwork	☐	☐		
Spell check	☐	☐		