Package leaflet: Information for the user

Extavia® 250 microgram/ml powder and solvent for solution for injection
interferon beta-1b

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

What is in this leaflet

1. What Extavia is and what it is used for

What Extavia is
Extavia is a type of medicine known as interferon used to treat multiple sclerosis. Interferons are proteins produced by the body that help it fight against attacks on the immune system such as viral infections.

How Extavia works
Multiple sclerosis (MS) is a long-term condition that affects the central nervous system (CNS), particularly the functioning of the brain and spinal cord. In MS, inflammation destroys the protective sheath (called myelin) around the nerves of the CNS and stops the nerves from working properly. This is called demyelination.

The exact cause of MS is unknown. An abnormal response by the body's immune system is thought to play an important part in the process which damages the CNS.

The damage to the CNS can occur within an MS attack (relapse). It can cause temporary disability, such as difficulty walking. Symptoms may disappear completely or partly.

Interferon beta-1b has been shown to change the response of the immune system and to help to reduce disease activity.

How Extavia helps fight your disease
Single clinical event indicating a high risk of developing multiple sclerosis: Extavia has been shown to delay progression to definite multiple sclerosis.

Relapsing-remitting multiple sclerosis: People with relapsing-remitting MS have occasional attacks or relapses during which symptoms become noticeably worse. Extavia has been shown to cut down the number of attacks and make them less severe. It reduces the number of hospital stays due to the disease and prolongs the time without relapses.

Secondary progressive multiple sclerosis: In some cases people with relapsing-remitting MS find that their symptoms increase and they progress to another form of MS called secondary progressive MS. With this, people find themselves becoming increasingly impaired, whether or not they have relapses. Extavia can reduce the number and severity of the attacks, and slow the progression of disability.

What Extavia is used for
Extavia is for use in patients
- ► **who have experienced for the first time symptoms which indicate a high risk of developing multiple sclerosis.** Your doctor will rule out any other reasons which could explain these symptoms before you are treated.
- ► **who suffer from relapsing-remitting multiple sclerosis, with at least two relapses within the last two years**.
- ► **who suffer from secondary progressive multiple sclerosis with active disease shown by relapses.**

2. What you need to know before you use Extavia

Do not use Extavia
- **if you are allergic** to natural or recombinant interferon beta, human albumin or any of the other ingredients of this medicine (listed in section 6).
- **if you currently suffer from severe depression and/or suicidal thoughts** (see "Warnings and precautions" and section 4, "Possible side effects").
- **if you have a severe liver disease** (see "Warnings and precautions", "Other medicines and Extavia" and section 4, "Possible side effects").

► **Tell your doctor,** if any of the above applies to you.

Warnings and precautions

Talk to your doctor before using Extavia:

- **If you have monoclonal gammopathy.** This is **a disorder of the immune system where an abnormal protein is found in the blood.** Problems with your small blood vessels (capillaries) may develop (systemic capillary leak syndrome) when using medicines like Extavia. This can lead to shock (collapse) and even be fatal.

- **If you have had depression or are depressed or previously had thoughts of suicide.** Your doctor will closely monitor you during treatment. If your depression and/or suicidal thoughts are severe, you will not be prescribed Extavia (see also "Do not use Extavia").

- **If you have ever had seizures or if you are taking medicines to treat epilepsy** (anti-epileptics), you doctor will monitor your treatment carefully (see also "Other medicines and Extavia" and section 4, "Possible side effects").

- **If you have severe kidney problems**, your doctor may monitor your kidney function during treatment.

- **If you have ever had an allergic reaction to latex.** The tip cap of the pre-filled syringe contains a derivative of natural rubber latex. Therefore, the tip cap may contain natural rubber latex.

Your doctor also needs to know the following **whilst you are using Extavia**:

- **If you experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath.** These may be symptoms of a serious allergic reaction, which may become life threatening.

- **If you feel noticeably more sad or hopeless than before the treatment with Extavia, or if you develop thoughts of suicide.** If you become depressed while you are on Extavia, you may need special treatment and your doctor will closely monitor you and may also consider stopping your treatment. If you suffer from severe depression and/or suicidal thoughts, you will not be treated with Extavia (see also "Do not use Extavia").

- **If you notice any unusual bruising, excessive bleeding after injury or if you seem to be catching a lot of infections**. These may be symptoms of a fall in your blood cell count or in the number of platelets in your blood (cells, which help the blood to clot). You may need extra monitoring by your doctor.

- **If you experience loss of appetite, tiredness, feeling sick (nausea), repeated vomiting, and especially if you notice widespread itching, yellowing of the skin or of the whites of the eyes, or easy bruising.** These symptoms may suggest problems with your liver. Changes to liver function values occurred in patients treated with Extavia during clinical studies. As for other beta interferons, severe liver damage, including cases of liver failure, have been reported rarely in patients taking Extavia. The most serious were reported in patients taking other medicines or who were suffering from diseases that can affect the liver (e.g. alcohol abuse, severe infection).

- **If you experience symptoms such as irregular heartbeat, swelling such as of the ankles or legs, or shortness of breath.** This may suggest a disease of the heart muscle (cardiomyopathy) which has been reported in patients using Extavia.

- **If you notice pain in your belly which is radiating to your back, and/or you feel sick or have a fever.** This may suggest an inflammation of the pancreas (pancreatitis), which has been reported with Extavia use. This is often associated with an increase in certain blood fats (triglycerides).

► **Stop using Extavia and tell your doctor immediately** if any of these happens to you.

Other things to consider when using Extavia:

- **You will need blood tests** to determine your blood cell count, blood chemistry and your liver enzymes. These will be performed **before you start using Extavia, regularly after treatment with Extavia has been initiated and then periodically during treatment,** even if you have no particular symptoms**.** These blood tests will be in addition to the tests which are normally done to monitor your MS.

- **If you have a heart disease, the flu-like symptoms which often occur at the start of treatment may prove stressful to you.** Extavia must be used with caution, and your doctor will monitor you for worsening of your heart condition, particularly at the start of treatment. Extavia itself does not affect the heart directly.

- **The functioning of your thyroid gland will be checked** regularly or whenever thought necessary by your doctor for other reasons.

- **Extavia contains human albumin and therefore carries a potential risk for transmission of viral diseases**. A risk of transmission of Creutzfeld-Jacob disease (CJD) cannot be ruled out.

- **During treatment with Extavia your body may produce substances called neutralising antibodies,** which may react with Extavia. It is not yet clear whether these neutralising antibodies reduce the effectiveness of the treatment. Neutralising antibodies are not produced in all patients. Currently it is not possible to predict which patients belong to this group.

- **During treatment with Extavia, kidney problems that may reduce your kidney function, including scarring (glomerulosclerosis), may occur.** Your doctor may perform tests to check your kidney function.

- **Blood clots in the small blood vessels may occur during your treatment**. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Extavia. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidneys.

Injection site reactions
During Extavia treatment you are likely to experience injection site reactions. Symptoms include redness, swelling, change in skin colour, inflammation, pain, and hypersensitivity. Skin breakdown and tissue damage (necrosis) around the injection site are reported less frequently. Injection site reactions usually become less frequent over time.

Injection site skin and tissue breakdown can result in scars forming. If this is severe a doctor may have to remove foreign matter and dead tissue (debridement) and, less often, skin grafting is required and healing may take up to 6 months.

To reduce the risk of getting injection site reaction you must:
– use a sterile (aseptic) injection technique,
– rotate the injection sites with each injection (see Annex Self-Injection procedure).

Injection site reactions may occur less frequently if you use an auto-injector device. Your doctor or nurse can tell you more about this.

If you experience any break in the skin, associated with swelling or fluid leaking out from the injection site:

► **Stop injecting Extavia** and talk to your doctor.

► **If you have only one sore injection site** (lesion) **and the tissue damage** (necrosis) **is not too extensive you may continue using Extavia.**

► **If you have more than one sore injection sites** (multiple lesions) you must stop using Extavia until your skin has healed.

Your doctor will regularly check the way you inject yourself, particularly if you have experienced injection site reactions.

Children and adolescents
There have been no formal clinical trials undertaken in children or adolescents.
However, there are some data available in adolescents aged from 12 to 17 years which suggest that the safety of Extavia in this group is the same as in adults. Extavia should not be used in children under 12 years of age as there is no information available for this age group.

Other medicines and Extavia
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

No formal interaction studies have been carried out to find out whether Extavia affects other medicines or is affected by them.

Using Extavia with other medicines that modify the immune system response is not recommended, except anti-inflammatory medicines called corticosteroids or the adrenocorticotropic hormone (ACTH).

Extavia should be used with caution with:
- **medicines which need a certain liver enzyme system** (known as cytochrome P450 system) for their removal from the body, for example medicines used to treat epilepsy (such as phenytoin).
- **medicines which affect the production of blood cells.**

Extavia with food and drink
Extavia is injected under the skin so any food or drink you consume is not thought to have any effect on Extavia.

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

No harmful effects on the breastfed newborn/infant are anticipated. Extavia can be used during breast-feeding.

Driving and using machines
Extavia may cause side effects in the central nervous system (see section 4 “Possible side effects”). If you are especially sensitive, this might influence your ability to drive or use machines.

Extavia contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium-free'.

3. How to use Extavia

Treatment with Extavia should be started under the supervision of a doctor who is experienced in the treatment of multiple sclerosis.

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

The recommended dose is every other day (once every two days), 1.0 ml of the prepared Extavia solution (see Annex “Self-injection procedure” in the second part of this leaflet) injected under the skin (subcutaneously). This equals 250 microgram (8.0 million IU) interferon beta-1b.

In general, treatment should be started at a low dose of 0.25 ml (62.5 microgram). Your doses will then be increased gradually to the full dose of 1.0 ml (250 microgram).
The dose should be increased at every fourth injection in four steps (0.25 ml, 0.5 ml, 0.75 ml, 1.0 ml). Your doctor may decide together with you to change the time intervals for dose increase depending on side effects you may experience at the start of treatment.

Preparing the injection
Before injection, the Extavia solution has to be prepared from a vial of Extavia powder and 1.2 ml of liquid from the pre-filled solvent syringe. This will either be done by your doctor or nurse or by yourself after you have been carefully trained.

Detailed instructions for self-injection of Extavia under the skin are provided in the Annex at the back of this leaflet. These instructions also tell you how to prepare the Extavia solution for injection.

The injection site must be changed regularly. See section 2 "Warnings and precautions" and follow the instructions under "Rotating injection sites" in the Annex at the back of this leaflet.

Duration of treatment
At present it is not known how long treatment with Extavia should last. **The length of treatment will be decided by your doctor together with you.**

If you use more Extavia than you should
Giving many times the dose of Extavia recommended for the treatment of multiple sclerosis has not led to life-threatening situations.

► **Talk to your doctor** if you inject too much Extavia or injected too often.

If you forget to use Extavia
If you have forgotten to give yourself an injection at the right time do it as soon as you remember and then follow on with the next one 48 hours later.

Do not inject a double dose to make up for a forgotten individual dose.

If you stop using Extavia
Talk to your doctor if you stop or wish to stop treatment. Stopping Extavia is not known to cause acute withdrawal symptoms.

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

4. Possible side effects

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

Extavia may cause serious side effects. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, pharmacist or nurse.

► **Tell your doctor immediately and stop using Extavia:**

- if you experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath.

- if you feel noticeably more sad or hopeless than before the treatment with Extavia, or if you develop thoughts of suicide.

- if you notice any unusual bruising, excessive bleeding after injury or if you seem to be catching a lot of infections.

- if you experience loss of appetite, tiredness, feeling sick (nausea), repeated vomiting, especially if you notice widespread itching, yellowing of the skin, or of the whites of the eyes or easy bruising.

- if you experience symptoms like irregular heart beat, swelling such as of the ankles or legs, or shortness of breath.

- if you notice pain in your belly which is radiating to your back , and/or you feel sick or have a fever.

► **Tell your doctor immediately:**

- if you get some or all of these symptoms: foamy urine, fatigue, swelling, particularly and the ankles and eyelids, and weight gain, as they may be signs of a possible kidney problem.

At the beginning of treatment side effects are common but in general they decrease with further treatment.

The most common side effects are:

► **Flu-like symptoms** such as fever, chills, painful joints, malaise, sweating, headache, or muscular pain. These symptoms may be reduced by taking paracetamol or non-steroidal anti-inflammatory medicines such as ibuprofen.

► **Injection site reactions.** Symptoms can be redness, swelling, discolouration, inflammation, pain, hypersensitivity, tissue damage (necrosis). See "Warnings and precautions" in section 2 for more information and what to do if you experience an injection site reaction. These may be reduced by the use of an auto-injector device. Talk to your doctor, pharmacist or nurse for further information.

To reduce the risk of side effects at the start of treatment, your doctor should start you on a low dose of Extavia and increase it gradually (see section 3, "How to use Extavia").

The following side effects listing is based on reports from clinical trials with Extavia (List 1) and from side effects reported on the marketed product (List 2).

List 1: Very common side effects which have occurred in clinical trials with Extavia (may affect more than 1 in 10 people) and at a higher percentage than those observed with placebo. The list also includes side effects which occurred commonly (may affect up to 1 in 10 people) but were significantly associated with the treatment:

- infection, abscess
- reduced number of white blood cells, swollen lymph glands (lymphadenopathy)
- decrease in the amount of sugar in the blood (hypoglycaemia)
- depression, anxiety
- headache, dizziness, sleeplessness, migraine, numbness or tingling feeling (paraesthesia)
- eye inflammation (conjunctivitis), abnormal vision
- ear pain
- irregular, rapid beating or pulsation of the heart (palpitation)
- redness and/or facial flushing due to widening of blood vessels(vasodilation), increased blood pressure (hypertension)
- runny nose, cough, hoarseness due to infection of the upper respiratory tract, sinusitis, cough increased, shortness of breath (dyspnoea)
- diarrhoea, constipation, nausea, vomiting, abdominal pain
- rises in the blood levels of liver enzymes (will show up in blood tests)
- skin disorder, rash
- muscle stiffness (hypertonia), painful muscles (myalgia), muscular debility (myasthenia), back pain, pain in extremities such as fingers and toes
- holding urine (urinary retention), protein in the urine (will show up in urine tests), urinary frequency, inability to hold back urination (urinary incontinence), urinary urgency
- painful periods (dysmenorrhoea), menstrual disorder, heavy uterine bleeding (metrorrhagia) especially between menstrual periods, impotence

- injection site reaction (including redness, swelling, discolouration, inflammation, pain, allergic reaction, see section 2 “Warnings and precautions”), skin breakdown and tissue damage (necrosis) at injection site (see section 2 “Warnings and precautions”)
- flu-like symptoms, fever, pain, chest pain, accumulation of fluid in arm, leg or face (peripheral oedema), lack/loss of strength (asthenia), chills, sweating, general feeling of being unwell.

In addition, the following side effects have been identified during post-marketing experience.

List 2: Side effects reported on the marketed product (frequencies - where known - based on clinical trials):

► **Very common (may affect more than 1 in 10 people):**

- painful joints (arthralgia).

► **Common (may affect up to 1 in 10 people):**

- the number of red cells in the blood may fall (anaemia),
- the thyroid gland does not work properly (too little hormone is produced) (hypothyroidism),
- weight increase or decrease,
- confusion,
- abnormally rapid heartbeat (tachycardia),
- a reddish yellow pigment (bilirubin), which is produced by your liver, may rise (this will show up in blood tests),
- swollen and usually itchy patches of skin or mucous membranes (urticaria),
- itching (pruritus),
- loss of scalp hair (alopecia),
- menstrual disorders (menorrhagia).

► **Uncommon (may affect up to 1 in 100 people):**

- the number of platelets (which help the blood to clot) may fall (thrombocytopenia),
- a certain type of blood fats (triglycerides) may increase (will show up in blood tests), see section 2 “Warnings and precautions”,
- suicide attempts,
- mood swings,
- convulsion,
- a specific liver enzyme (gamma GT) which is produced by your liver, may rise (this will show up in blood tests),
- inflammation of the liver (hepatitis),
- skin discolouration.

► **Rare (may affect up to 1 in 1,000 people):**

- serious allergic (anaphylactic) reactions,
- the thyroid gland does not work properly(thyroid disorders), too much hormone is produced (hyperthyroidism),
- inflammation of the pancreas (pancreatitis), see section 2 “Warnings and precautions”,
- blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.

Side effects derived only during post marketing:

- kidney problems including scarring (glomerulosclerosis) that may reduce your kidney function, (uncommon).
- severe loss of appetite leading to weight loss (anorexia), (rare).
- disease of the heart muscle (cardiomyopathy), (rare).
- sudden shortness of breath (bronchospasm), (rare).
- the liver does not work properly (hepatic injury [including hepatitis], hepatic failure), (rare).
- problems with your small blood vessels (capillaries) may develop when using medicines like Extavia (systemic capillary leak syndrome), (frequency unknown).
- rash, redness of the skin in the face, joint pain, fever, weakness and others caused by the medicine (drug-induced lupus erythematosus), frequency unknown.
- severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs (*pulmonary arterial hypertension*), (frequency unknown). Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Extavia.

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 (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Ireland:	HPRA Pharmacovigilance Website: www.hpra.ie
Malta:	ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal
United Kingdom:	Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

5. How to store Extavia

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

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

Do not store above 25°C. Do not freeze.

After preparing the solution you should use it immediately. However, if you are not able to do so, it will remain usable for a period of 3 hours, if kept in a refrigerator (2°C - 8°C).

Do not use this medicine if you notice it contains particles or is discoloured.

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

6. Contents of the pack and other information

What Extavia contains
- The active substance is interferon beta-1b. Each vial contains 300 microgram (9.6 million IU) interferon beta-1b per vial. After reconstitution, each millilitre contains 250 microgram (8.0 million IU) interferon beta-1b.
- The other ingredients are
  - in the powder: mannitol and human albumin.
  - in the solvent: sodium chloride, water for injection.

The tip cap of the pre-filled syringe contains a derivative of natural rubber latex. Therefore, the tip cap may contain natural rubber latex.

What Extavia looks like and contents of the pack
Extavia is a powder and solvent for solution for injection.

The powder is white to off-white in colour.
The Extavia powder is provided in a 3-millilitre vial.
The solvent is a clear/colourless solution.
The solvent for Extavia is provided in a 2.25 ml pre-filled syringe and contains 1.2 ml sodium chloride 5.4 mg/ml (0.54% w/v) solution for injection.

Extavia is available in pack sizes of:
- 5 vials of interferon beta-1b and 5 pre-filled syringes containing solvent.
- 14 vials of interferon beta-1b and 14 pre-filled syringes containing solvent.
- 15 vials of interferon beta-1b and 15 pre-filled syringes containing solvent.
- 14 vials of interferon beta-1b and 15 pre-filled syringes containing solvent.

- 3-month multipack containing 42 (3x14) vials of interferon beta-1b and 42 (3x14) pre-filled syringes containing solvent.
- 3-month multipack containing 45 (3x15) vials of interferon beta-1b and 45 (3x15) pre-filled syringes containing solvent.
- 3-month multipack containing 42 (3x14) vials of interferon beta-1b and 45 (3x15) pre-filled syringes containing solvent.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Pharma GmbH
Roonstrasse 25
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Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Novartis Ireland Limited
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Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

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Other sources of information

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

Annex: SELF-INJECTION PROCEDURE

The following instructions and pictures explain how to prepare Extavia for injection and how to inject Extavia yourself. Please read the instructions carefully and follow them step by step. Your doctor or nurse will help you to learn the process of self-administration. Do not attempt to inject yourself until you are sure that you understand how to prepare the injection solution and give the injection to yourself.

PART I: STEP BY STEP INSTRUCTIONS

The instructions include the following main steps:

A) General advice
B) Getting ready to inject
C) Reconstituting and drawing up the solution for injection, step by step
D) Making the injection manually (to make an injection with the ExtaviPro 30G auto-injector, refer to the instructions for use provided with the auto-injector)

A) General advice

- **Getting off to a good start!**

You will find that within a few weeks your treatment will become a natural part of your routine. As you get started, you may find the following tips helpful:

- Set up a permanent storage area in a convenient location out of the sight and reach of children so that your Extavia and other supplies are always easy to find.
  For details on storage conditions see section 5 of the leaflet, “How to store Extavia”.

- Try to give yourself the injection at the same time each day. This makes it easier to remember and easier to plan a block of time when you will not be interrupted.
  Please refer to section 3 of the leaflet, “How to use Extavia”, for further details on how to use Extavia.

- Prepare each dose only when you are ready for an injection. After mixing Extavia, you should administer the injection immediately (if this medicine is not used immediately, see section 5 of the leaflet, “How to store Extavia”).

- **Important tips to keep in mind**

- Be consistent - use this medicine as described in section 3 of the leaflet, “How to use Extavia”. Always double-check your dosage.
- Keep your syringes and syringe disposal unit out of the sight and reach of children; lock the supplies away if possible.
- Never re-use syringes or needles.
- Always use a sterile (aseptic) technique as described in here.
- Always place the used syringes in the proper disposal unit.

B) Getting ready to inject

- **Choosing an injection site**

Before preparing your injection, decide where you are going to inject. You should inject this medicine into the fatty layer between the skin and muscle (that is, subcutaneously, about 8 mm to 12 mm under the skin). The best places for injections are where the skin is loose and soft, and away from joints, nerves and bones, for example the abdomen, arm, thigh or buttocks.

Important:

The tip cap of the pre-filled syringe contains a derivative of natural rubber latex. Therefore, the tip cap may contain natural rubber latex. If you are allergic to latex, talk to your doctor before using Extavia.

Do not use any area where you can feel lumps, bumps, firm knots, pain or an area that is discoloured, indented, scabbed, or where the skin is broken. Talk to your doctor or nurse about these or any other unusual conditions you may find.

You should rotate the injection site at every injection. If some areas are too difficult for you to reach, you may need a family member or friend to help you with these injections. Follow the sequence described in the schedule at the end of the Annex (see Part II "Rotating injection sites") and you will come back to your first injection site area after 8 injections (16 days). This will give each injection site a chance to fully recover before receiving another injection.

Please refer to the rotation schedule at the end of this Annex to learn how to choose an injection site. An example of a medication record is also included (see Annex Part III). This should give you an idea of how you can keep track of your injection sites and dates.

- **Medicine**

You will need the medicine:

- 1 Extavia vial (with powder for solution for injection)
- 1 pre-filled syringe of solvent for Extavia (sodium chloride solution)

To reconstitute and inject your medicine you will need to use an ExtaviPro 30G application kit (supplied separately to your medicine), which contains the following components and instructions on how to use them:

- Vial adapters for use when reconstituting your medicine
- 30-gauge needles for injecting your medicine
- Alcohol swabs

You will also need a disposal unit for used syringes and needles.

The 30-gauge needles provided with the application kit for the administration of this medicine can be used either for manual injection **OR** with an ExtaviPro 30G auto-injector.

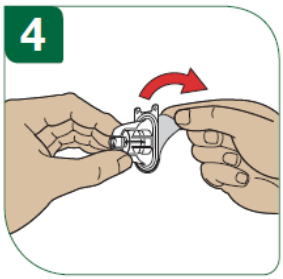
For skin disinfection use an appropriate disinfectant recommended by your pharmacist.

C) Reconstituting and drawing up the solution for injection, step by step

1 - Wash your hands thoroughly with soap and water before beginning this process.

2 - Remove the flip off cap from the Extavia vial. It is best to use your thumb rather than your nail, as your nail could break. Put the vial on the table.

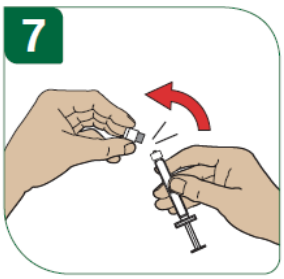
3 - Clean the top of the vial with an alcohol swab, moving the swab in one direction only. Leave the swab on top of the vial.



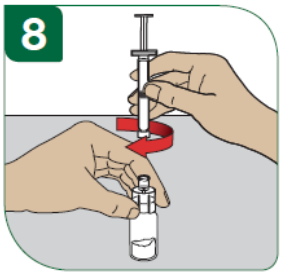
4 - Peel back and remove the cover from the vial adapter packaging. **Do not remove the vial adapter from its packaging.**

5 - Remove the swab from the top of the vial.
Use the packaging to handle the vial adapter. Attach it to the vial by pushing down until the vial adapter penetrates and locks around the top of the vial.

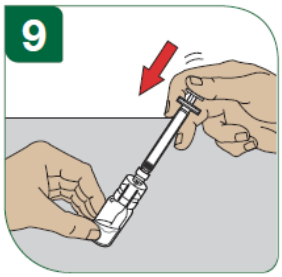
6 - Holding the edges securely, remove and discard the packaging **ensuring the vial adapter remains on the vial.**



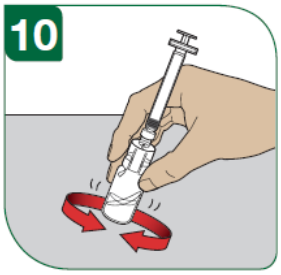
7 - Take out the pre-filled solvent syringe from its package. Snap off and discard the tip of the syringe.
Note: Be careful not to touch the exposed end of the syringe. Do not push the plunger.



8 - Holding the vial and adapter securely, screw the syringe fully onto the vial adapter.
This forms the syringe-vial assembly.

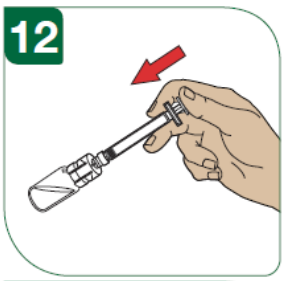


9 - Hold the syringe-vial assembly at a slight angle. Push the plunger down slowly so that the liquid runs down the inside of the vial.
Transfer **all** the solvent to the vial.
Note: Do not shake the vial as this may cause excessive foaming.

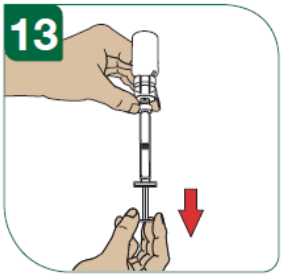


10 - Hold the vial between your thumb and fingers. Swirl the syringe-vial assembly gently until the powder is completely dissolved.
Note: Do not shake the vial.

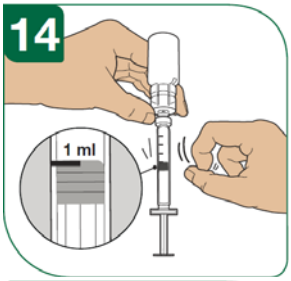
11 - Examine the solution carefully. It should be clear and contain no particles.
Note: If the solution is discoloured or contains particles, discard it and start again with a new syringe and vial from your package.
If excessive foaming is present – which can happen if the vial is shaken or swirled too vigorously – let the vial sit undisturbed until the foam settles.



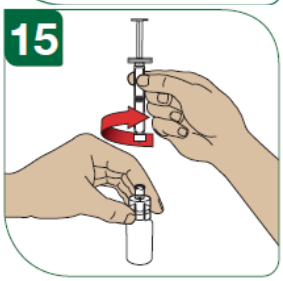
12 - Ensure the plunger stays fully pushed in before proceeding to the next step, as it may have moved.



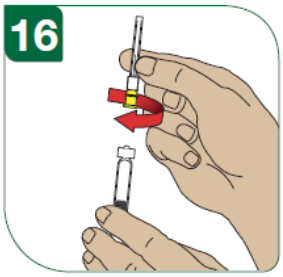
13 - Turn the syringe-vial-assembly so that the vial is at the top. Slowly pull the plunger back to draw all of the solution into the syringe.



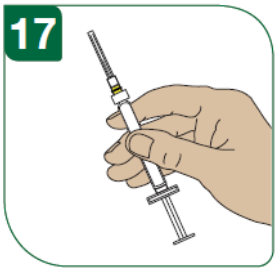
14 - Remove any excess air bubbles by gently tapping the syringe. Push the plunger to the **1 ml** mark (or to the volume prescribed by your doctor).
Note: It may be necessary to adjust the plunger position back and forth a few times to ensure the excess air bubbles are gone and there is 1 ml of solution in the syringe.



15 - Unscrew the syringe, leaving the vial adapter on the vial. Dispose of the vial and the remaining unused portion of the solution into the disposal unit.



16 - Take the needle out of its wrapping and screw it firmly onto the top of the syringe.

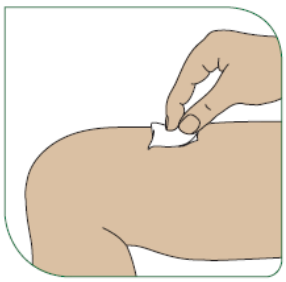


17 - Leave the needle cap on. You are now ready to manually inject yourself or to use the ExtaviPro 30G auto-injector for the administration of Extavia.

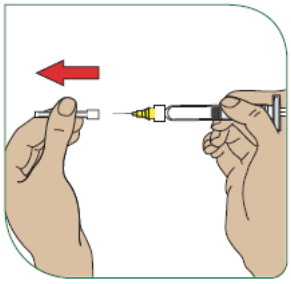
Storage after reconstitution
If, for some reason, you are not able to inject Extavia immediately, you can refrigerate the reconstituted solution for up to 3 hours before using it. Do not freeze the solution, and do not wait longer than 3 hours to inject it. **If more than 3 hours pass, discard the medicine and prepare a new injection.** When you use the solution, warm it up by holding the syringe or vial in your hands before injecting to avoid pain.

D) Making the injection manually (to make an injection with the ExtaviPro 30G auto-injector, refer to the instructions for use provided with the auto-injector)

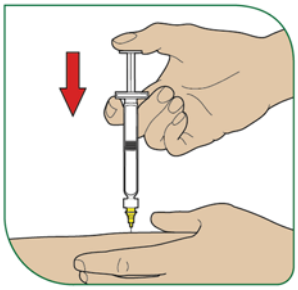
1 - Choose a site for the injection (refer to the section “Choosing an injection site” and the diagrams at the end of this leaflet) and make a note of it in your medication record.



2 - Use an alcohol swab to clean the skin at the injection site. Let the skin air-dry. Throw the swab away.



3 - Remove the cap from the needle by pulling and not twisting it.



4 - Where possible gently pinch the skin together around the disinfected injection site (to raise it up a little).

5 - Holding the syringe like a pencil or a dart, push the needle straight into the skin at a 90˚ angle with a quick, firm motion.

6 - Inject the medicine (by pushing the plunger slowly and steadily all the way in until the syringe is empty).

7 - Discard the syringe in the disposal unit.

PART II: ROTATING INJECTION SITES

You need to choose a new site for each injection to allow the area time to recover and help prevent infection. Advice on which areas to choose is given in the first part of this Annex. It is a good idea to know where you plan to inject before you prepare your syringe. The schedule shown in the diagram below will help you to vary the sites appropriately. For example, give the first injection into the right side of the abdomen, choose the left side for the second injection, then move to the right thigh for the third, and so on through the diagram until all suitable areas of the body have been used. Keep a record of where and when you last gave yourself an injection. One way to do that is to note the injection site on the enclosed medication record card.

By following this schedule, you will come back to your first area (e.g. the right side of the abdomen) after 8 injections (16 days). This is called a Rotation Cycle. On our example schedule each area is split again into 6 injection sites (which adds up to 48 injection sites altogether), left and right: upper, middle and lower part of each area. If you come back to an area after one Rotation Cycle choose the most distant injection site within this area. If an area becomes sore, talk to your doctor or nurse about choosing other injection sites.

Rotation schedule

To help you rotate the injection sites appropriately, we recommend that you keep a record of the date and location of your injection. You can use the following rotation schedule.

Work through each rotation cycle in turn. Each cycle will be 8 injections (16 days), given in area 1 through to area 8 in turn. By following this sequence, you will give each area a chance to recover before receiving another injection.

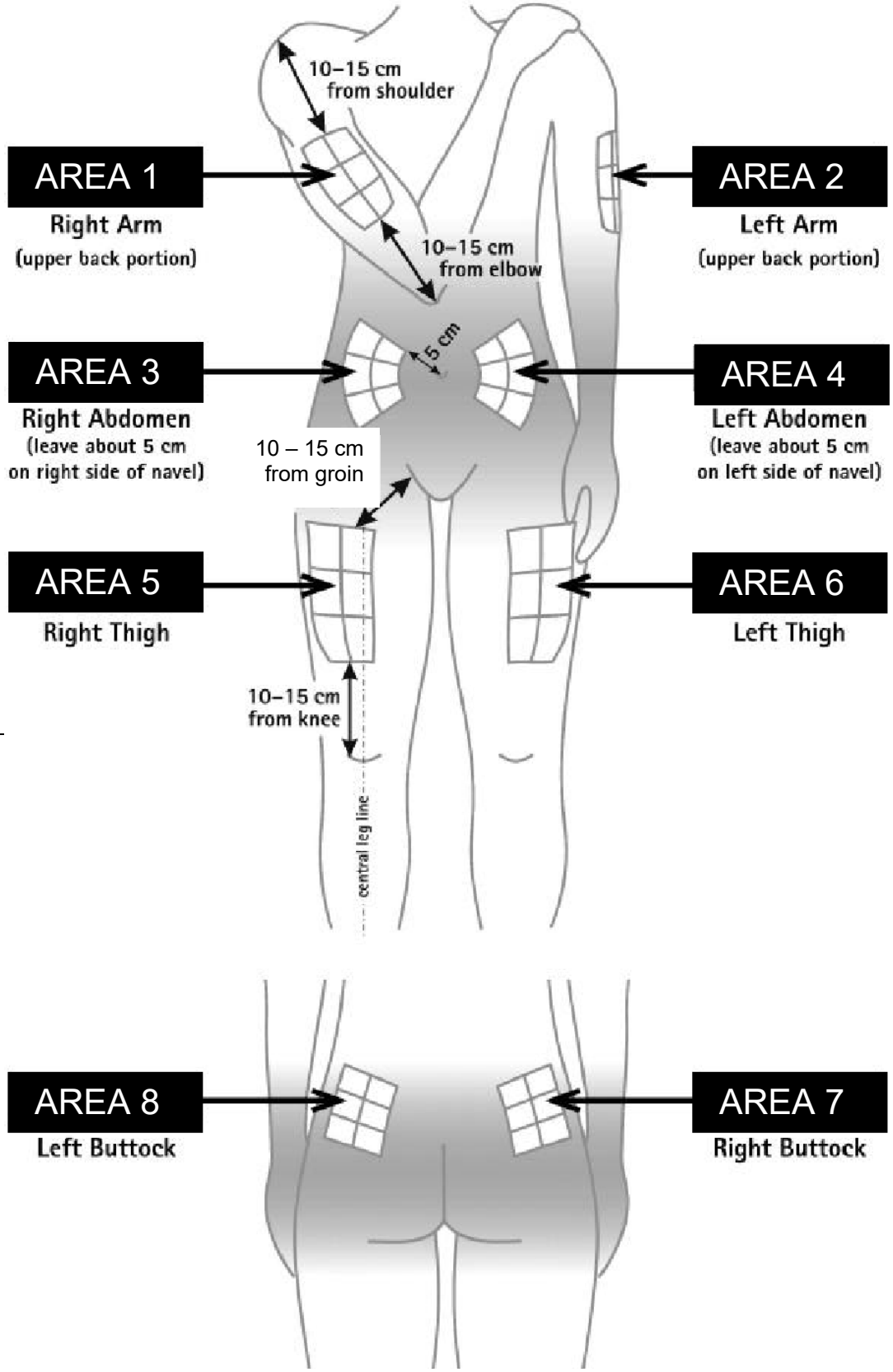
Rotation Cycle 1: Upper left section of each area
Rotation Cycle 2: Lower right section of each area
Rotation Cycle 3: Middle left section of each area
Rotation Cycle 4 Upper right section of each area
Rotation Cycle 5: Lower left section of each area
Rotation Cycle 6: Middle right section of each area

PART III: EXTAVIA Medication record

Instructions for keeping track of your injection sites and dates

- Start with your first injection (or your last injection if you are not a new Extavia user).
- Select an injection site. If you have already been using Extavia start with the area that has not been used during the last rotation cycle (i.e. the past 16 days).
- After your injection, fill in the used injection site and date in the table in your injection record (see the example: Keeping track of your injection sites and dates).

ROTATION SCHEDULE:



EXAMPLE OF A MEDICATION RECORD: