CONTAINS PARACETAMOL

Package leaflet: Information for the user

IXPRIM® effervescent 37.5 mg/325 mg effervescent tablets

Tramadol hydrochloride/Paracetamol

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, please 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 or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:

1. What IXPRIM is and what it is used for

IXPRIM is a combination of two analgesics, tramadol hydrochloride and paracetamol, which act together to relieve your pain.

IXPRIM is intended for use in the treatment of moderate to severe pain when your doctor recommends that a combination of tramadol hydrochloride and paracetamol is needed.

IXPRIM should only be taken by adults and adolescents over 12 years.

2. What you need to know before you take IXPRIM

Do not take IXPRIM

- if you are allergic to tramadol hydrochloride, paracetamol, sunset yellow or any of the other ingredients of this medicine (listed in section 6);
- in acute poisoning with alcohol, sleeping pills, pain relievers or other psychotropic medicines (medicines that affect mood and emotions);
- if you are also taking MAO inhibitors (certain medicines used for treatment of depression or Parkinson's disease) or have taken them in the last 14 days before treatment with IXPRIM;
- if you suffer from a severe liver disorder;
- if you have epilepsy that is not adequately controlled on your current medicine.

Warnings and precautions
Talk to your doctor before taking IXPRIM, if:

- you take other medicines containing paracetamol or tramadol hydrochloride;
- you have liver problems or liver disease or if you notice your eyes and skin turning yellow. This may suggest jaundice or problems with your bile ducts.
- you have kidney problems;
- you have severe difficulties in breathing for example asthma or severe lung problems;
- you have epilepsy or have already experienced fits or seizures;
- you suffer from depression and you are taking antidepressants as some of them may interact with tramadol (see "Other medicines and IXPRIM");
- you have recently suffered from a head injury, shock or severe headaches associated with vomiting;
- you are dependent on any medicines including those used to relieve pain, for example morphine;
- you take other medicines to treat pain that contain buprenorphine, nalbuphine or pentazocine;
- you are going to have an anaesthetic. Tell your doctor or dentist that you are taking IXPRIM.

Tolerance, dependence, and addiction
This medicine contains tramadol which is an opioid medicine. Repeated use of opioids can result in the drug being less effective (you become accustomed to it, known as tolerance). Repeated use of IXPRIM can also lead to dependence, abuse and addiction, which may result in life-threatening overdose. The risk of these side effects can increase with a higher dose and longer duration of use.

Dependence or addiction can make you feel that you are no longer in control of how much medicine you need to take or how often you need to take it.
The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent on or addicted to IXPRIM if:
- you or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- you are a smoker.
- you have ever had problems with your mood (depression, anxiety, or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.

If you notice any of the following signs whilst taking IXPRIM, it could be a sign that you have become dependent or addicted:
- you need to take the medicine for longer than advised by your doctor
- you need to take more than the recommended dose
- you are using the medicine for reasons other than prescribed, for instance, 'to stay calm' or 'help you sleep'
- you have made repeated, unsuccessful attempts to quit or control the use of the medicine
- When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again ('withdrawal effects').

If you notice any of these signs, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to stop safely (See section 3, If you stop taking IXPRIM).

During treatment with IXPRIM, tell your doctor straight away if:
you have severe illnesses, including severe renal impairment or sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), or you suffer from malnutrition, chronic alcoholism or if you are also taking flucloxacillin (an antibiotic). A serious condition called metabolic acidosis (a blood and fluid abnormality) has been reported in patients in these situations when paracetamol is used at regular doses for a prolonged period or when paracetamol is taken together with flucloxacillin. Symptoms of metabolic acidosis may include: serious breathing difficulties with deep rapid breathing, drowsiness, feeling sick (nausea) and being sick (vomiting).

Sleep-related breathing disorders

IXPRIM contains an active substance that belongs to the group of opioids. Opioids can cause sleep-related breathing disorders, for example central sleep apnea (shallow/pause of breathing during sleep) and sleep-related hypoxemia (low level of oxygen in the blood).
The risk of experiencing central sleep apnea is dependent on the dose of opioids. Your doctor may consider decreasing your total opioid dosage if you experience central sleep apnea.

There is a small risk that you may experience a so-called serotonin syndrome that can occur after having taken tramadol in combination with certain antidepressants or tramadol alone. Seek medical advice immediately if you have any of the symptoms related to this serious syndrome (see section 4 "Possible side effects").

Tramadol is transformed in the liver by an enzyme. Some people have a variation of this enzyme and this can affect people in different ways. In some people, they may not get enough pain relief but other people are more likely to get serious side effects. If you notice any of the following side effects, you must stop taking this medicine and seek immediate medical advice: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation, lack of appetite.

If any of the above-mentioned points applied to you in the past or applies to you while you are taking IXPRIM, please make sure your doctor knows. He/she can then decide whether you should continue to use this medicine.

Children and adolescents
Use in children with breathing problems:
Tramadol is not recommended in children with breathing problems, since the symptoms of tramadol toxicity may be worse in these children.

Talk to your doctor if you experience any of the following symptoms while taking IXPRIM:
Extreme fatigue, lack of appetite, severe abdominal pain, nausea, vomiting or low blood pressure.
This may indicate that you have adrenal insufficiency (low cortisol levels) If you have these symptoms, contact your doctor, who will decide if you need to take hormone supplement.

Other medicines and IXPRIM

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Important: This medicine contains paracetamol and tramadol hydrochloride. Tell your doctor if you are taking *any other medicine containing paracetamol or tramadol hydrochloride*, so that you do not exceed the maximum daily doses.

You **must not** take IXPRIM together with monoamine oxidase inhibitors ("MAOIs") (see section "Do not take IXPRIM").

IXPRIM is not recommended to be taken with the following:

- carbamazepine (a medicine commonly used to treat epilepsy or some types of pain such as severe pain attacks in the face called trigeminal neuralgia).
- buprenorphine, nalbuphine or pentazocine (opioid-type pain relievers). The pain-relieving effect may be reduced.

Please inform your doctor or pharmacist if you are taking:
- flucloxacillin (antibiotic), due to a serious risk of blood and fluid abnormality (called metabolic acidosis) that must have urgent treatment (see section 2) High anion gap metabolic acidosis is a serious disease that must have urgent treatment.

The risk of side effects increases, if you are taking:

- triptans (for migraine) or selective serotonin re-uptake inhibitors, "SSRIs" (for depression). If you experience confusion, restlessness, fever, sweating, uncoordinated movement of limbs or eyes, uncontrollable jerking of muscles or diarrhoea you should call your doctor.
- other pain relievers such as morphine and codeine (also as cough medicine), baclofen (a muscle relaxant) medicines used to lower blood pressure or medicines to treat allergies. You may feel drowsy or feel faint. If this happens, tell your doctor.
  Concomitant use of IXPRIM and sedative medicines such as benzodiazepines or other sedatives or medicines that impair breathing activity (e.g. opioids) increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However if your doctor prescribes IXPRIM together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
  Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.
- medicines which may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk having a fit may increase if you take IXPRIM at the same time. Your doctor will tell you whether IXPRIM is suitable for you.
- certain antidepressants, IXPRIM may interact with these medicines and you may experience serotonin syndrome (see section 4 "Possible side effects").
- warfarin or phenprocoumon (for blood thinning). The effectiveness of such medicines may be altered and bleeding may occur. Any prolonged or unexpected bleeding should be reported to your doctor immediately.
- Gabapentin or pregabalin to treat epilepsy or pain due to nerve problems (neuropathic pain).
- medicines used to treat allergies, travel sickness or nausea (antihistamines or antiemetics).
- medicines to treat psychiatric disorders (antipsychotics or neuroleptics).
- muscle relaxants.
- medicines to treat Parkinson's disease.

The effectiveness of IXPRIM may be altered if you also take

- metoclopramide, domperidone or ondansetron (medicines for treatment of nausea and vomiting),
- cholestyramine (medicine to reduce cholesterol in the blood),

Your doctor will tell you which medicines are safe to take with IXPRIM.

Taking IXPRIM with food and alcohol
IXPRIM may make you feel drowsy. Alcohol may make you feel drowsier, so it is best not to drink alcohol while you are taking IXPRIM.

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

As IXPRIM contains tramadol hydrochloride, you should not take this medicine during pregnancy or breast-feeding. If you become pregnant during treatment with IXPRIM, please consult your doctor before taking any further tablets.

Breast-feeding
Tramadol is excreted into breast milk. For this reason, you should not take IXPRIM more than once during breast-feeding, or alternatively, if you take IXPRIM more than once, you should stop breast-feeding.
Based on human experience tramadol is suggested not to influence female or male fertility. No data on the influence of the combination of tramadol and paracetamol on fertility are available.

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

Driving and using machines
IXPRIM may make you feel drowsy and this may affect your ability to drive, or use tools and machines, safely.

IXPRIM contains Sunset yellow E110, sodium and sulphite

The medicinal product contains the colorant Sunset yellow E110 which may cause allergic reactions.

This medicinal product contains 179.3 mg sodium (main component of cooking/ table salt) in each effervescent tablet. This is equivalent to 9.0% of the recommended maximum daily dietary intake of sodium for an adult. Talk to your doctor or pharmacist if you need 2 or more tablets daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

The orange flavour in this medicinal product contains low amounts of sulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

3. HOW TO TAKE IXPRIM

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting treatment and regularly during treatment, your doctor will discuss with you what you may expect from using IXPRIM, when and how long you need to take it, when to contact your doctor, and when you need to stop it (see also section 2).

You should take IXPRIM for as short a time as possible.
The use in children below the age of 12 years is not recommended.

The dosage should be adjusted to the intensity of your pain and your individual pain sensitivity. In general the lowest pain-relieving dose should be taken.

The recommended starting dose, unless otherwise prescribed by your doctor, is 2 effervescent tablets for adults and adolescents over 12 years.

If required, further doses may be taken, as recommended by your doctor. The shortest time between doses must be at least 6 hours.

Do not take more than 8 IXPRIM effervescent tablets per day.
Do not take IXPRIM more often than your doctor has told you.

Older people
In older patients (above 75 years) the excretion of tramadol may be delayed. If this applies to you, your doctor may recommend prolonging the dosage interval.

Severe liver or kidney disease (insufficiency) /dialysis patients
Patients with severe liver and/or kidney insufficiency should not take IXPRIM. If in your case the insufficiency is mild or moderate, your doctor may recommend prolonging the dosage interval.

Method of administration:
The effervescent tablets are for oral use.
Effervescent tablets should be taken dissolved in a glass of drinking water.

If you think that the effect of IXPRIM is too strong (i.e. you feel very drowsy or have difficulty breathing) or too weak (i.e. you have inadequate pain relief), contact your doctor.

If you take more IXPRIM than you should:
In such cases please contact your doctor or pharmacist immediately even if you feel well.
After taking very high doses, pin-point pupils, vomiting, fall in blood pressure, fast heart beat, collapse, disturbed consciousness up to coma (deep unconsciousness), epileptic fits, and difficulty in breathing up to cessation of breathing and death may occur. In such cases a doctor should be called immediately.

An overdose of paracetamol can cause nausea and vomiting. There is a risk of liver damage which may only show later. Severe cases may lead to liver failure, brain issues, coma, or death.

If you forget to take IXPRIM:
If you forget to take the effervescent tablets, pain is likely to return. Do not take a double dose to make up for forgotten individual doses, simply continue taking the effervescent tablets as before.

If you stop taking IXPRIM:
You should not suddenly stop taking this medicine unless your doctor tells you to. If you want to stop taking your medicine, discuss this with your doctor first, particularly if you have been taking it for a long time. Your doctor will advise you when and how to stop, which may be by lowering the dose gradually to reduce the chance of developing unnecessary side effects (withdrawal symptoms).

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

4. Possible side effects

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

Very common: may affect more than 1 in 10 people
- nausea,
- dizziness, drowsiness.

Common: may affect up to 1 in 10 people
- vomiting, digestion problems (constipation, flatulence, diarrhoea), stomach pain, dry mouth,
- itching, sweating (hyperhidrosis),
- headache, shaking,
- confusional state, sleep disorders, mood changes (anxiety, nervousness, a feeling of high spirits).

Uncommon: may affect up to 1 in 100 people
- increase in pulse or blood pressure, heart rate or heart rhythm disorders,
- tingling, numbness or feeling of pins and needles in the limbs, ringing in the ear, involuntary muscle twitching,
- depression, nightmares, hallucination (hearing, seeing or sensing things that are not really there), memory lapses,
- difficulty breathing
- difficulty swallowing, blood in the stools,
- skin reactions (for example rashes, hives),
- increase in liver enzyme values,
- presence of albumin in urine, difficulties or pain on passing urine,
- shivering, hot flushes, pain in the chest.

Rare: may affect up to 1 in 1,000 people
- fits, difficulties in carrying out coordinated movements, transient loss of consciousness (syncope),
- drug dependence,
- delirium,
- vision blurred, constriction of the pupils (miosis)
- speech disorders,
- excessive dilation of the pupils (mydriasis).

Unknown: frequency not known
- decrease in blood sugar level.

The following are recognised side effects which have been reported by people using medicines that contain only tramadol hydrochloride or only paracetamol. However, if you experience any of these while taking IXPRIM, you should tell your doctor:
- feeling faint when getting up from a lying or sitting position, slow heart rate, fainting, changes in appetite, muscle weakness, slower or weaker breathing, mood changes, changes in activity, changes in perception, worsening of existing asthma.
- Use of IXPRIM together with medicines used to thin the blood (e.g. phenprocoumon, warfarin) may increase the bleeding risk. Any prolonged or unexpected bleeding should be reported to your doctor immediately.
- In some rare cases a skin rash, indicating an allergic reaction, may develop with sudden swelling of the face and neck, difficulties breathing or drop of blood pressure and fainting. If this happens to you, stop treatment and see a doctor immediately. You must not take the medicine again.

In rare cases, using a medicine of the type of tramadol hydrochloride may make you become dependent on it, making it hard to stop taking it.
On rare occasions, people who have been taking tramadol hydrochloride for some time may feel unwell if they stop treatment abruptly. They may feel agitated, anxious, nervous or shaky. They may be hyperactive, have difficulty sleeping and have stomach or bowel disorders. Very few people may also get panic attacks, hallucinations, unusual perceptions such as itching, tingling and numbness, and noise in the ears (tinnitus). If you experience any of these complaints after stopping IXPRIM, please consult your doctor.
- Frequency not known: hiccups.

Serotonin syndrome, that can manifest as mental status changes (e.g. agitation, hallucinations, coma), and other effects, such as fever, increase in heart rate, unstable blood pressure, involuntary twitching, muscular rigidity, lack of coordination and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) (see section 2 “What you need to know before you take IXPRIM”).

In exceptional cases blood tests may reveal certain abnormalities, for instance, low counts of blood platelets, which may result in nose bleeds or bleeding gums.

Very rare cases of serious skin reactions have been reported with paracetamol.

Rare cases of respiratory depression have been reported with tramadol.

A serious condition that can make blood more acidic (called metabolic acidosis), in patients with severe illness using paracetamol (see section 2) with an unknown frequency.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects via HPRA Pharmacovigilance Website: www.hpra.ie. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE IXPRIM

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

Store this medicine in a safe and secure storage space, where other people cannot access it. It can cause serious harm and be fatal to people when it has not been prescribed for them.

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

Packed in strips of coated aluminium foil:
Do not store above 25° C.

Do not throw away any medicines via waste water 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 IXPRIM contains

- The active substances are tramadol hydrochloride and paracetamol.
  One effervescent tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol.

- The other ingredients are:

  Monosodium citrate anhydrous, citric acid anhydrous, Povidone K30, sodium hydrogen carbonate, Macrogol 6000, silica colloidal anhydrous, magnesium stearate, Flavour Orange (maltodextrin (maize), modified starch (E1450), natural and artificial flavourings, sulphite), acesulfame potassium, saccharin sodium, Sunset yellow (E110)

What IXPRIM looks like and contents of the pack

IXPRIM effervescent tablets are off white to slightly rosy coloured with some coloured speckles.
The tablets are packed in strips of coated aluminium foil.

IXPRIM comes in boxes of 2, 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 effervescent tablets packed in aluminium strips.

Not all pack sizes will be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Grünenthal Pharma Ltd.
4045 Kingswood Road
Citywest Business Park
Citywest
Co. Dublin
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Manufacturer:
Grünenthal GmbH
Zieglerstraße 6,
D-52078 Aachen

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This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

France	Ixprim® 37,5mg/325mg, comprimé effervescent Zaldiar® 37,5mg/325mg, comprimé effervescent
Hungary	Zaldiar® 37.5 mg/325 mg, pezsgőtabletta
Ireland	Ixprim® effervescent 37.5 mg/325 mg, effervescent tablet
Portugal	Zaldiar® EFE 37,5mg/325 mg comprimidos efervescentes
Slovenia	Zaldiar® 37,5 mg/325 mg šumeče tablete
Spain	Zaldiar® 37,5 mg/325 mg comprimidos efervescentes
United Kingdom (NI)	Tramacet® 37.5 mg/325 mg effervescent tablet

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