Package leaflet: Information for the user

Carlosafine 35 micrograms/h transdermal patch
Carlosafine 52.5 micrograms/h transdermal patch
Carlosafine 70 micrograms/h transdermal patch

buprenorphine

- **These patches contain a strong pain killer**
- **Ensure that old patches are removed before applying a new one**
- **Patches must not be cut**
- **Do not expose the patches to a heat source (such as a hot water bottle)**
- **Do not soak in a hot bath or take a hot shower whilst wearing a patch.**
- **If you develop a fever tell your doctor immediately**
- **Follow the dosage instructions carefully and only change your patch twice a week on the chosen times.**
- **If your breathing becomes shallow and weak take the patch off and seek medical help**

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 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 Carlosafine is and what it is used for
2. What you need to know before you use Carlosafine
3. How to use Carlosafine
4. Possible side effects
5. How to store Carlosafine
6. Contents of the pack and other information

1. What Carlosafine is and what it is used for

The active substance of Carlosafine is buprenorphine.

Carlosafine is an analgesic (a pain-relieving medicine) intended to relieve moderate to severe cancer pain and severe pain that has not responded to other types of painkillers. Carlosafine acts through the skin. When the transdermal patch is applied to the skin, the active substance buprenorphine passes through the skin into the blood. Buprenorphine is an opioid (strong pain reliever), which reduces pain by acting on the central nervous system (specific nerve cells in the spinal cord and in the brain). The effect of the transdermal patch lasts for up to four days. Carlosafine is not suitable for the treatment of acute (short-lasting) pain.

2. What you need to know before you use Carlosafine

Do not use Carlosafine
- if you are allergic to buprenorphine or any of the other ingredients of this medicine (listed in section 6);
- if you are dependent on strong pain relievers (opioids);
- if you suffer from a disease in which you have or may have great difficulty breathing
- if you are taking monoamine oxidase (MAO) inhibitors (certain medicines used to treat depression) or you have taken this type of medicine in the last two weeks (see " Other medicines and Carlosafine");

- if you suffer from myasthenia gravis (a certain type of severe muscle weakness);
- if you suffer from delirium tremens (confusion and trembling caused by abstinence from alcohol following habitual excessive drinking or occurring during an episode of heavy alcohol consumption);
- if you are pregnant.

Carlosafine must not be used to treat withdrawal symptoms in drug-dependent persons.

Warnings and precautions

Take special care with Carlosafine
- if you have recently drunk a lot of alcohol;
- if you suffer from seizures or convulsions (fits)
- if your consciousness is disturbed (feeling light-headed or faint) for an unknown reason;
- if you are in a state of shock (cold sweat might be a sign of it);
- if the pressure in your skull is increased (for instance after head injury or in brain disease), and artificial respiration is not possible;
- if you have difficulty breathing or are taking other medicines that may make you breathe more slowly or weakly (see "Other medicines and Carlosafine");
- if you have depression or other conditions that are treated with antidepressants. The use of these medicines together with Carlosafine can lead to serotonin syndrome, a potentially life-threatening condition (see “Other medicines and Carlosafine”).
- if your liver does not work properly;
- if you are inclined to abuse medicines or drugs.

Tolerance, dependence, and addiction

This medicine contains buprenorphine 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 Carlosafine 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 Carlosafine 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 Carlosafine, 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 might feel that you need to carry on taking your medicine, even when it doesn’t help to relieve your pain.
- 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 using 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 using Carlosafine).

Also, please be aware of the following precautions:
- Fever and external heat may lead to larger quantities of buprenorphine in the blood than normal. Also, external heat may prevent the transdermal patch from sticking properly. Therefore, do not expose yourself to external heat (e.g. sauna, infra-red lamps, electric blankets, hot water bottles) and consult your doctor if you have fever.

Athletes should be aware that this medicine may cause a positive reaction to sports doping control tests.

Sleep-related breathing disorders
Carlosafine can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

Children and adolescents
Carlosafine should not be used in persons below the age of 18 years, because no experience has so far been gained in this age group.

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

- Carlosafine must not be used together with monoamine oxidase (MAO) inhibitors (certain medicines used to treat depression), or if you have taken this type of medicine for the last 2 weeks.
- Carlosafine may make some people feel drowsy, sick, or faint or make them breathe more slowly or weakly. These side effects may be intensified if other medicines that may produce the same effects are taken at the same time. These other medicines include other strong pain relievers (opioids), certain sleeping pills, anaesthetics, and medicines used to treat certain psychological diseases such as tranquillizers, anti-depressants, and neuroleptics, gabapentin or pregabalin to treat epilepsy or pain due to nerve problems (neuropathic pain)

Please inform your doctor or pharmacist if you are taking:
- medicines 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.

Concomitant use of Carlosafine and sedating medicines such as benzodiazepines or related drugs 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 does prescribe Carlosafine together with sedating medicines the dose and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all sedating 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.

- If Carlosafine is used together with some medicines, the effects of the transdermal patch may be increased. These medicines include e.g. certain anti-infectives/anti-fungals (e.g. containing erythromycin or ketoconazole) or HIV medicines (e.g. containing ritonavir)
- If Carlosafine is used together with other medicines, the effects of the transdermal patch may be reduced. These medicines include certain products, e.g. dexamethasone; medicines to treat epilepsy (e.g. containing carbamazepine, or phenytoin) or medicines for tuberculosis (e.g. rifampicin).

- Some medicines may increase the side effects of Carlosafine and may sometimes cause very serious reactions. Do not take any other medicines whilst taking Carlosafine without first talking to your doctor, especially anti-depressants, such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepine, or trimipramine. These medicines may interact with Carlosafine and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, hallucinations, coma, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C. Contact your doctor when experiencing such symptoms.

Carlosafine with food, drink and alcohol

You should not drink alcohol while using Carlosafine. Alcohol may intensify certain side effects of the transdermal patch and you may feel unwell. Drinking grapefruit juice may intensify the effects of Carlosafine.

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 using this medicine.

There is not sufficient experience regarding the use of Carlosafine in pregnant women. Therefore, you do not use Carlosafine if you are pregnant.

Buprenorphine, the active substance contained in the transdermal patch, inhibits milk formation and passes into the breast milk. Therefore, do not use Carlosafine if you are breast-feeding.

Driving and using machines
Carlosafine may make you feel dizzy or drowsy or experience blurred or double vision and affect your reactions to such an extent that you may not react adequately or quickly enough in the event of unexpected or sudden occurrences. This applies particularly
- at the beginning of treatment,
- when your dosage is changed,
- when you switch to Carlosafine from another pain reliever,
- if you also use other medicines that act on the brain,
- if you drink alcohol.

Carlosafine can affect your ability to drive as it may make you sleepy or dizzy.
- Do not drive while taking this medicine until you know how it affects you.
- It is an offence to drive if this medicine affects your ability to drive.
- However, you would not be committing an offence if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and

- It was not affecting your ability to drive safely

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

If you are affected, you should not drive or operate machinery whilst using Carlosafine. This applies also at the end of treatment with Carlosafine. Do not drive or operate machinery for at least 24 hours after the patch has been removed.

Discuss with your doctor or pharmacist if you are unsure about anything.

3. How to use Carlosafine

Always use this medicine exactly as your doctor has told you. 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 Carlosafine, when and how long you need to take it, when to contact your doctor, and when you need to stop it (see also, If you stop using Carlosafine).

Carlosafine is available in three strengths: Carlosafine 35 micrograms/h transdermal patch, Carlosafine 52.5 micrograms/h transdermal patch and Carlosafine 70 micrograms/h transdermal patch.

The choice of which strength of Carlosafine will suit you best will be made by your doctor. During treatment your doctor may change which transdermal patch you use to a smaller or larger one if necessary.

Always use Carlosafine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The recommended dose is:

Adults

Unless your doctor has told you differently, attach one Carlosafine transdermal patch (as described in detail below) and change it after 4 days at the latest. For convenience of use, you can change the transdermal patch twice a week at the same days, e.g. always on Monday mornings and Thursday evenings. To help you remember when to change your transdermal patch, you should make a note on the calendar on the outer packaging. If your doctor has advised you to take other pain relievers in addition to the transdermal patch, strictly follow the doctor's instructions, otherwise you will not fully benefit from treatment with Carlosafine.

Use in children and adolescents

Carlosafine should not be used in persons below the age of 18 years, because no experience has so far been gained in this age group.

Elderly patients

No dosage adjustment is needed for elderly patients.

Patients with kidney disease / dialysis patients

In patients with kidney disease and in dialysis patients, no dosage adjustment is necessary.

Patients with liver disease

In patients with liver disease, the intensity and duration of action of Carlosafine may be affected. If this applies to you, your doctor will check on you more closely.

Route of administration

The patch is for transdermal use.

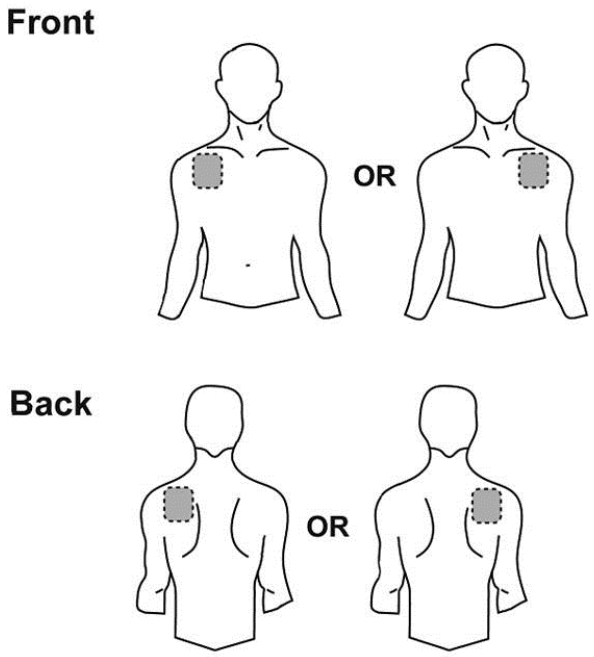
When the transdermal patch is applied to the skin, the active substance buprenorphine passes through the skin into the blood.

Method of administration

The following table shows you when to change your patch:

Apply/change your patch in the morning		**Apply/change your patch in evening of**
Monday	⇄	Thursday
Tuesday	⇄	Friday
Wednesday	⇄	Saturday
Thursday	⇄	Sunday
Friday	⇄	Monday
Saturday	⇄	Tuesday
Sunday	⇄	Wednesday

Before applying the transdermal patch

- Choose an area of skin which is flat, clean and hairless on your upper body, preferably on the chest below the collar-bone or on the upper part of the back (see adjacent illustrations). Call assistance if you cannot apply the transdermal patch yourself.	

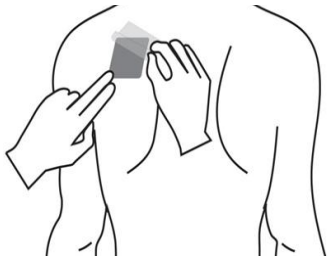
- If the chosen area has hairs, cut them off with a pair of scissors. Do not shave them off!
- Avoid skin which is red, irritated or has any other blemishes, for instance large scars.
- The area of skin you choose must be dry and clean. If necessary, wash it with cold or lukewarm water. Do not use soap or other detergents. After a hot bath or shower, wait until your skin is completely dry and cool. Do not apply lotion, cream or ointment to the chosen area. This might prevent your transdermal patch from sticking properly.

Applying the transdermal patch

- Step 1: Each transdermal patch is sealed in a sachet. Just before use, cut the sachet along the sealed edge with scissors. Take out the transdermal patch.

- Step 2: The sticky side of the transdermal patch is covered with a transparent protective foil. Carefully peel off **one part of** the foil. Try not to touch the sticky part of the transdermal patch.

- Step 3: Stick the transdermal patch onto the area of skin you have chosen and remove the remaining foil.



- Step 4: Press the transdermal patch against your skin with the palm of your hand for about 30 to 60 seconds. Make sure that the whole transdermal patch is in contact with your skin, especially at the edges.

- Step 5: Wash your hands after using the transdermal patch. Do not use any cleansing products.

Wearing the transdermal patch

You may wear the transdermal patch for up to 4 days. Provided that you have applied the transdermal patch correctly, there is little risk of it coming off. You may shower, bathe or swim while wearing it. However, do not expose the transdermal patch to extreme heat (e.g. sauna baths, infra-red lamps, electric blankets, hot water bottles).

In the unlikely event that your transdermal patch falls off before it needs changing, do not use the same transdermal patch again. Stick a new one on straight away (see "Changing the transdermal patch" below).

Changing the transdermal patch

- Take the old transdermal patch off.

- Fold it in half with the sticky side inwards.
- Throw it away carefully, out of the sight and reach of children**.**
- Stick a new transdermal patch on a different skin site (as described above). Wait at least one week before using the same site again.

Duration of treatment
Your doctor will tell you how long you may use Carlosafine. Do not stop using Carlosafine on your own account, because pain may return and you may feel unwell (see also "If you stop using Carlosafine" below).

If you have the impression that the effect of the Carlosafine transdermal patch is too weak or too strong, tell your doctor or pharmacist.

If you use more Carlosafine than you should
If this happens there may be signs of an overdose of the substance buprenorphine. An overdose may intensify the side effects of buprenorphine such as drowsiness, nausea, and vomiting. You may get pin-point pupils and breathing may become slow and weak. You may also get cardiovascular collapse. An overdose can potentially lead to coma and death.

As soon as you discover that you have used more transdermal patches than you should, remove the excess transdermal patches and talk to a doctor or pharmacist.

If you forget to use Carlosafine
If you forget an application, stick a new transdermal patch on as soon as you remember. You will then need to change your routine, e.g. if you usually apply your transdermal patches on Mondays and Thursdays, but you forget and don't stick on a new transdermal patch until Wednesday, you will need to change your transdermal patches on Wednesdays and Saturdays from then on. Make a note of the new pair of days on the calendar on the outer packaging. If you are very late changing your transdermal patch, pain may return. In this case please contact your doctor.

Never apply twice the number of transdermal patches to make up for the forgotten application!

If you stop using Carlosafine
If you interrupt or finish using Carlosafine too soon, pain may return. If you wish to stop use on account of unpleasant side effects, please consult your doctor. He/she will tell you what can be done and whether you can be treated with other medicines.

Some people may experience withdrawal-effects when they have used strong pain relievers for a long time and stop using them. The risk of having effects after you stop using Carlosafine is very low. However, if you feel agitated, anxious, nervous or shaky, if you are overactive, have difficulty sleeping or digestion problems, tell your doctor.

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.

Side effects are classified as follows:

Very common: more than 1 out of 10 persons	Common: more than 1 out of 100 persons and less than 1 out of 10 persons
Uncommon: more than 1 out of 1000 persons and less than 1 out of 100 persons	Rare: more than 1 out of 10000 persons and less than 1 out of 1000 persons
Very rare:	Not known:

less than 1 out of 10,000 persons	frequency cannot be estimated from the available data

The following side effects have been reported:

Immune system disorders
Very rare: serious allergic reactions (see below)

Metabolism and nutrition disorders
Rare: loss of appetite

Psychiatric disorders
Uncommon: confusion, sleep disorder, restlessness

Rare: illusions such as hallucinations, anxiety and nightmares, reduced sex drive

Very rare: dependence, mood swings

Nervous system disorders
Common: dizziness, headache

Uncommon: various degrees of sedation (calmness), ranging from tiredness to muzziness

Rare: difficulty concentrating, speech disorder, muzziness, disturbed balance, abnormal skin sensations (numbness, prickling or
burning sensations)

Very rare: muscle twitching, taste disorders

Eye disorders

Rare: visual disturbance, blurred vision, swollen eyelids

Very rare: pin-point pupils

Ear disorders

Very rare: ear pain

Heart and blood circulation disorders

Uncommon: circulatory disorders (such as low blood pressure or, rarely, even circulatory collapse)

Rare: hot flushes

Chest and lung disorders

Common: shortness of breath

Rare: difficulty breathing (respiratory depression)

Very rare: abnormally rapid breathing, hiccups

Digestive system disorders

Very common: nausea (feeling sick)

Common: vomiting, constipation

Uncommon: dry mouth

Rare: heartburn

Very rare: retching

Skin disorders (generally at the site of application)

Very common: redness, itching

Common: skin changes (exanthema, generally on repeated use), sweating

Uncommon: rash

Rare: hives

Very rare: pustules, small blisters

Not known: dermatitis contact (skin rash with inflammation which may include burning sensation, skin discolouration).

Urinary system disorders

Uncommon: difficulty in passing water, urine retention (less urine than normal)

Reproductive system disorders

Rare: erection difficulties

General disorders

Common: oedema (e.g. swelling of the legs), tiredness

Uncommon: weariness

Rare: withdrawal symptoms (see below), administration site reactions
Very rare: chest pain

If you notice any of the side effects listed above, tell your doctor as soon as possible.

In some cases delayed allergic reactions occurred with marked signs of inflammation. In such a case you should stop using Carlosafine after you have talked to your doctor.

If you experience swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing, hives, fainting, yellowing of the skin and eyes (also called jaundice), remove the transdermal patch and call your doctor immediately or seek help at the casualty department of the nearest hospital. These can be symptoms of a very rare serious allergic reaction.

Some people may have withdrawal symptoms when they have used strong pain relievers for a long time and stop using them. The risk of having withdrawal effects when you stop using Carlosafine is low. However, if you feel agitated, anxious, nervous or shaky, if you are overactive, have difficulty sleeping or digestion problems, tell your doctor.

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

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 directly via Yellow Card Scheme Website: 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 Carlosafine

- **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 carton and sachet after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Store this medicine in a safe and secure place, where other people cannot access it. It can cause serious harm and be fatal to people who may take this medicine by accident, or intentionally when it has not been prescribed for them.
- After removing a patch, fold it in half with the sticky sides inwards and press them together. Return the used patch to its sachet and carefully dispose the transdermal patch.
- 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 Carlosafine contains
- The active substance is buprenorphine.

[35 micrograms /h:]
Each transdermal patch of 25 cm^2 contains 20 mg of buprenorphine and releases 35 micrograms of buprenorphine per hour.
[52.5 micrograms /h:]
Each transdermal patch of 37.5 cm^2 contains 30 mg of buprenorphine and releases 52.5 micrograms of buprenorphine per hour.
[70 micrograms /h:]
Each transdermal patch of 50 cm^2 contains 40 mg of buprenorphine and releases 70 micrograms of buprenorphine per hour.

- The other ingredients are:

Adhesive matrix (containing buprenorphine): povidone K90, levulinic acid, oleyl oleate, Poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinylacetate] (5:15:75:5)

Adhesive matrix (without buprenorphine): Poly[(2-ethylhexyl)acrylate-co-glycidylmethacrylate-co-(2-hydroxyethyl)acrylate-co-vinylacetate] (68:0,15:5:27),
Separating foil between adhesive matrices with and without buprenorphine: Polyethylene terephthalate film,
Backing foil: polyester,
Release liner: Polyethylene terephthalate film, siliconised
Blue printing ink

What Carlosafine looks like and contents of the pack

Each transdermal patch is rectangular beige coloured with rounded corners and is imprinted
[35 µg/h:]
"Buprenorphin" and "35 µg/h"
[52.5 µg/h:]
"Buprenorphin" and "52.5 µg/h"
[70 µg/h:]
"Buprenorphin" and "70 µg/h"

Each transdermal patch is sealed in one child-resistant sachet. The patches are available in packs containing 4, 5, 8, 10, 16 or 20 transdermal patches.

Not all pack sizes may be marketed.

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