

**Package Leaflet: Information for the user**  
**Difene Ampoules 75 mg / 3 ml**  
**Solution for Injection or Concentration for Solution for Infusion**  
**(diclofenac sodium)**

**Read all of this leaflet carefully before you start using this medicine.**

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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**1. What Difene is and what it is used for** Difene ampoules contain diclofenac sodium as the active ingredient, which is a non-steroidal anti-inflammatory drug (NSAID). This means that it is a “painkilling” medicine which reduces inflammation and swelling, but it does not contain any steroid medicine. Difene ampoules are for intramuscular injection (IM) or preparation of intravenous infusion (IV).

**Intramuscular use (IM):**

Difene can be used in the management of aggravated rheumatoid arthritis and osteoarthritis, in acute back pain, acute gout, post-operative pain, relief of pain in acute traumatic musculo-skeletal disorders and fractures and for abdominal pain commonly caused by kidney stones.

**Intravenous infusion (IV):**

For treatment or prevention of post-operative pain in the hospital setting.

**2. What you need to know before you use Difene Do not take Difene:**

- if you are allergic (hypersensitive) to diclofenac or any of the other ingredients of Difene ampoules. Please refer to section 6 of this leaflet for full list of ingredients of Difene.
- If you have ever had an allergic reaction (skin rash, difficulty in breathing or runny nose) to aspirin (acetylsalicylic acid) or any other NSAID such as ibuprofen.
- if you have had any gastrointestinal problems after taking any other NSAID, e.g. vomiting blood or passing black, tarry stools.
- if you have or have ever suffered from a stomach ulcer or bleeding from the stomach.
- if you have severe heart failure.
- if you have severe kidney failure or liver failure.
- if you are in the last three months of pregnancy - please see section on ‘Pregnancy and breastfeeding’.

- Do not give this medicine to children up to 3 years.

If any of these apply to you, tell your doctor or pharmacist. Your doctor will decide whether this medicine is suitable for you.

### **Warning and Precautions with Difene**

#### **Speak to your doctor before receiving**

#### **Difene if you:**

- have experienced asthma, allergic inflammation of the nasal airways
- if any skin rash develops such as hives or itchy skin
- have experienced symptoms of chronic obstructive pulmonary diseases (COPD), shortness of breath, persistent cough
- have high blood pressure
- have heart problems
- have mild to moderate heart failure
- have liver or kidney problems
- have severe liver or kidney disease
- suffer from a disorder of your metabolism such as porphyria
- suffer from any bowel problems such as ulcerative colitis or Crohn's disease
- suffer from an upset stomach or irritation of the gut
- have suffered from any blood disorder or bleeding disorder such as haemophilia
- are pregnant or think you may become pregnant
- are breast-feeding
- are elderly
- have peripheral arterial disease (signs and symptoms of this are pain and numbness in the arms and legs)
- have cerebrovascular disease, this is a condition that develops as a result of problems with blood vessels in the brain. If you have a history of strokes or mini strokes please speak to your doctor
- have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes, high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist
- have recently had major surgery

If any of these apply to you, tell your doctor or pharmacist. Your doctor will decide whether this medicine is suitable for you.

Non-steroidal anti-inflammatory drugs (NSAIDs) can cover the signs and symptoms of an infection.

Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.

You may also be prescribed a medicine to protect the lining of the stomach while taking diclofenac

Patients who are using Difene long-term and patients with severe liver impairment will undergo monitoring during the use of Difene.

It is advised to use the lowest dose for the shortest time to reduce the likelihood of side-effects.

If you have asthma, hayfever (seasonal allergic rhinitis), swelling of the nasal mucosa (nasal polyps), narrowing of the airways (due to a condition known as chronic obstructive pulmonary disease) or chronic infections of the respiratory tract (e.g. chest infections and especially allergic symptoms affecting the nose) you are more likely to experience reactions to NSAIDs (e.g. diclofenac). These reactions could include worsening of asthma (often referred to as intolerance to analgesics/analgesics asthma), development of hives on the skin and swelling of the eyes and lips and mucous membranes; You may be at greater risk of developing these reactions to NSAIDs if you are already allergic to, and have had reactions to, other substances. A doctor's supervision and extreme precaution is advised with the use of NSAIDs if you have any allergic condition as described here that could predispose you to an allergic reaction.

**Medicines such as diclofenac may be associated with a small increased risk of heart attack (“myocardial infarction”) or stroke.**

### **Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you are taking other medicines, make sure your doctor is aware of them, particularly if they are any of the following:

- other anti-inflammatory or “painkilling” medicines (NSAIDs)
- water tablets (diuretics)
- steroids which are used as the main treatment for certain inflammatory conditions (corticosteroids)
- aspirin (anti-platelet agents)
- medicines used to thin the blood such as warfarin (anticoagulants)
- mood stabilizing drugs such as lithium
- immunosuppressive agents which are drugs that inhibit or prevent activity of the immune system (ciclosporine)
- medicines which may be used to treat cancer (methotrexate)
- medicines for heart conditions or high blood pressure (beta blockers, ACE inhibitors, digoxin)
- quinolone antibiotics (ciprofloxacin, ofloxacin)
- aminoglycosides antibiotics used in serious infections (streptomycin)
- tablets to treat diabetes
- medicines for the treatment of gout (probenecid)
- medicines for the treatment of depression (selective serotonin re-uptake inhibitors) e.g. fluoxetine, paroxetine
- an anticoagulant such as heparin
- treatment of hypertension and congestive heart failure (angiotensin-receptor blockers)
- if taking tablets to relieve the symptoms of inflammation and pain (COX inhibitors)
- medicine for epilepsy (phenytoin)
- cholesterol medication (colestipol)
- medicine used to reduce bile acid (cholestyramine)
- medicine used for gout (sulfapyrazone)
- antifungal medication (voriconazole)

If you are presently taking any of these medicines and are unsure talk to your doctor or pharmacist.

### **Pregnancy, breastfeeding and fertility**

Do not receive Difene if you are pregnant or breast-feeding unless it is considered essential by your doctor.

Difene may make it more difficult to become pregnant. You should inform your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

This medicine must not be used by women who are in the last three months of pregnancy. Ask your doctor for advice before taking any medicine.

### **Driving and using machines**

Difene should not affect your ability to drive or operate machinery. If in the unlikely event you have dizziness or blurred vision, do not drive or operate machinery.

### **Important information about some of the ingredients of Difene**

Difene ampoules solution contains less than 1 mmol sodium (23 mg) per 3 ml, i.e. essentially 'sodium-free'.

Difene Ampoules contain benzyl alcohol. This must not be given to premature babies or neonates. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.

### **3. How to use Difene**

The doctor or nurse will ensure that you receive this medicine as prescribed by your doctor.

- Difene ampoules are for intramuscular injection or the preparation of intravenous infusion.
- Difene ampoules for intramuscular use should not be mixed with other injection solutions.
- It is important that you use the lowest dose that controls your pain and you should not use Difene longer than necessary.

#### **Adults:**

##### **Intramuscular use (IM)**

- The usual dosage for adults is one 75 mg ampoule once daily (or in severe cases twice daily) intramuscularly into the buttock. It is advised that the alternative buttock be used for the second injection. Difene ampoules should not be given for more than 2 days. Treatment can be continued with capsules or suppositories.

Renal colic: One 75 mg ampoule intramuscularly. A further ampoule may be administered after 30 minutes if necessary. As with oral Difene the total daily dose should not exceed 150 mg.

##### **Intravenous use (IV)**

- The contents of the ampoules will be diluted before being given into a vein over a period of at least 30 minutes. A second dose may be administered 8 hours after the first infusion. A maximum of two doses may be given. Your doctor has carefully chosen the correct dosage for you, taking into account the severity of your condition, your age and any other reasons special to you.

#### **Elderly:**

The dosage should be kept as low as possible.

**Children:**

Not recommended in children.

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

**4. Possible side effects**

Like all medicines, Difene can cause side effects, although not everybody gets them. These may occur in the initial stages of treatment and may be more serious if they occur in the elderly.

**If the following happens at any time during your treatment, tell your doctor immediately:**

- an allergic reaction (swelling of the lips, face or neck leading to severe difficulty in breathing, skin rash or hives)
- passing blood in your faeces (stools)
- passing black tarry stools
- vomiting any blood or dark particles that look like coffee grounds
- a serious illness with blistering of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome)
- indigestion or heartburn
- abdominal pain (pains in your stomach) or other abnormal stomach symptoms.

These are very serious side effects. You may need urgent medical attention or hospitalisation. The frequency of the side effects listed below is defined using the following convention:

*Very common ( $\geq 1/10$ );*

*Common ( $\geq 1/100$  to  $< 1/10$ )*

*Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )*

*Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )*

*Very Rare ( $< 1/10,000$ )*

*Not Known (cannot be estimated from available data).*

**Common:**

- Headache, dizziness
- Vertigo
- Nausea, vomiting, diarrhoea, indigestion, flatulence, abdominal pain, loss of appetite
- Skin rash
- Injection site reaction which can include redness, tenderness, warmth and itching
- Injection site pain
- Hardening of skin at injection site
- Increased levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGTP), enzymes that are normally present in liver and heart cells, SGOT and SGTP are released into blood when the liver or heart are damaged.

**Rare:**

- Allergic reactions (e.g. difficulties in breathing, wheezing or low blood pressure)
- Drowsiness, tiredness

- Asthma, shortness of breath
- Inflammation of the lining of the stomach
- Any sign of bleeding in the stomach or intestine, for example, when emptying your bowels
- Gastro-intestinal ulcers with or without bleeding
- Yellowing of your skin or the whites of your eyes (hepatitis or liver function disorders)
- Hives
- Injection site necrosis (destruction and death of the skin surrounding the site of injection)
- Fluid retention

***Very Rare:***

- Decrease of platelets in the blood, signs of this can be bleeding inside the body or bleeding from the skin
- Decrease of white blood cells in the blood
- Anaemia, abnormal bleeding
- Rapid swelling , including swelling of the face
- Disorientation, depression, insomnia, nightmares, irritability, psychotic disorder.
- Sensation of tingling, pricking, or numbness of skin
- Impaired memory
- Convulsions, tremors
- Anxiety
- Symptoms of aseptic meningitis with neck stiffness, headaches, nausea, vomiting or clouding of consciousness
- Impaired sense of taste
- Loss of appetite
- Lesions in the food pipe
- Stroke
- Visual disturbances (blurred and double vision)
- Hearing loss, tinnitus (ringing in the ears)
- Palpitations, chest pain
- Cardiac failure
- Heart attack
- High blood pressure
- Inflammatory destruction of blood vessels, symptoms of which can be fever and weight loss
- Inflammation of lung tissue
- Swelling of the large intestine
- Crohn's disease
- Inflammation of the pancreas
- Constipation
- Inflammation of the mucous lining in the mouth
- Swollen tongue and colour change of the tongue
- Reflux, heartburn
- Fulminant hepatitis
- Liver failure

- Eczema
- Reddening of the skin
- Abscess at injection site
- Skin diseases known as Steven Johnson syndrome and Lyell's, which are the detachment of top layers of skin from bottom layers
- Inflammation of scaling of skin
- Loss of hair
- Photosensitivity reactions, abnormal responses to sunlight or artificial light
- Purpura, the appearance of red or purple discolouration on the skin
- Allergic reaction of unknown origin causing red patches on the skin
- Kidney failure, signs and symptoms of this are bloody stools, fatigue, bruising easily and fluid retention
- Blood in the urine
- Excess protein in your urine which can cause your urine to become foamy
- Nephrotic syndrome, which is a disorder in which the kidneys can become damaged the most common signs of this are weight gain due to excess fluid retention, swelling, and foamy urine
- Interstitial nephritis, which is a kidney disorder in which the spaces between the kidney tubules become swollen (inflamed). Some symptoms of this condition may be blood in urine, fever, nausea and vomiting
- Renal papillary necrosis, which is a disorder of the kidneys, symptoms of this may be back pain blood in urine, cloudy urine.

Gastrointestinal bleeding associated with this product can be fatal.

**If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.**

**5. How to store Difene Keep out of the reach and sight of children.**

Store in the original pack. Do not store above 25°C. Store in the original package to protect from light and moisture. For single use only. Discard any remaining contents. Do not use after the expiry date as stated on the label and carton. The expiry date refers to the last day of the month. Standard precautions for disposal of glass ampoules should be followed.

Medicines should not be disposed of via wastewater. These measures will help to protect the environment.

Do not use Difene ampoules if you notice visible signs of deterioration.

The shelf life after dilution for IV infusion:

The product should be used immediately. If not used immediately, in-use storage times and condition as prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

**6. Contents of the pack and other information What Difene contains**

Each ampoule contain 25 mg/ml of diclofenac sodium. The active substance is diclofenac sodium. The other ingredients are water for injections, propylene glycol, benzyl alcohol 105 mg / 3 ml, mannitol, acetylcysteine and sodium hydroxide.

**What Difene looks like and contents of the pack**

Difene ampoules are a clear colourless solution for injection presented in colourless glass ampoules in a clear plastic tray, one or two trays per box.  
Difene are available in packs of 5 or 10 ampoules.  
Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder:**

Astellas Pharma Co. Ltd  
5 Waterside,  
Citywest Business Campus,  
Naas Road, Dublin 24,  
Ireland

**Manufacturer:**

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