Package leaflet: Information for the patient

Combogesic 10 mg/ml Paracetamol + 3 mg/ml Ibuprofen solution for infusion

paracetamol/ibuprofen

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- You should not use this medicine for longer than 2 days.

What is in this leaflet

1. What Combogesic is and what it is used for

Combogesic contains the active substances paracetamol and ibuprofen. Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (or NSAIDs). Paracetamol works in a different way to ibuprofen, but both substances work together to reduce pain.

Combogesic is used in adults for the short-term symptomatic treatment of acute moderate pain, where an intravenous route of administration is necessary and/or when other routes of administration are not possible.

2. What you need to know before you are given Combogesic

You should not be given Combogesic:
- if you are allergic to the active substances, other NSAIDs, or any of the other ingredients of this medicine (listed in section 6);
- if you have severe heart failure, liver failure or kidney failure;
- if you regularly drink large quantities of alcohol;
- if you have asthma, urticaria or allergic-type reactions after taking acetylsalicylic acid or other NSAIDs;
- if you have a history with gastrointestinal bleeding or perforation related to previous NSAID therapy;
- if you have or have had an active or recurrent peptic ulcer (i.e. stomach or duodenal ulcer), or bleeding (two or more distinct episodes of proven ulceration or bleeding);

- if you have bleeding of the brain (cerebrovascular bleeding) or other active bleeding;
- if you have a blood clotting disorder or increased tendency to bleeding;
- if you have severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake);
- during the last three months of pregnancy;
- if you are under the age of 18 years.

Warnings and precautions

In order to avoid the risk of overdose,

– check that other medicines do not contain paracetamol,

– do not exceed the maximum recommended doses (see section 3).

Side effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms. Do not use Combogesic for more than 2 days.

Talk to your doctor or nurse before you are given Combogesic if:

- you are taking any other medicines containing paracetamol, ibuprofen, or any other anti-inflammatory (NSAID) painkillers (in order to avoid the risk of an overdose);
- you have heart problems including heart failure, angina pectoris (chest pain), or if you have had a heart attack, bypass surgery, peripheral artery disease (poor circulation in the legs or feet due to narrow or blocked arteries), or any kind of stroke (including 'mini-stroke' or transient ischaemic attack "TIA").
- you have high blood pressure, diabetes, high cholesterol, have a family history of heart disease or stroke, or if you are a smoker;
- you have liver disease, hepatitis, kidney disease or difficulty urinating;
- you currently have an infection; Combogesic may hide the symptoms or signs of an infection (fever, pain and swelling);
- you have or had previously had heartburn, indigestion, stomach ulcer or any other stomach problems;
- you have recently had or plan to have surgery;
- you have an infection (see heading "Infections" below);
- you have asthma;
- you are dehydrated or have diarrhoea;
- you have bowel or intestinal problems such as ulcerative colitis or Crohn's Disease;
- you have an inherited genetic or acquired disorder of certain enzymes that manifests with either neurological complications or skin problems or occasionally both, i.e. porphyria;
- you have an autoimmune disease such as Lupus erythematosus or other connective tissue disorders, as there may be an increased risk of aseptic meningitis (inflammation of the protective membrane surrounding the brain);
- you suffer from hay fever, nasal polyps or chronic obstructive respiratory disorders since there may be an increased risk of allergic reactions;
- you are pregnant or intend to become pregnant (see section Pregnancy, breast-feeding and fertility).

Cardiovascular risk

Anti-inflammatory/pain-killer medicines like ibuprofen may be associated with a small increased risk of heart attack or stroke, particularly when used at high doses. Do not exceed the recommended dose or duration of treatment.

Gastrointestinal symptoms
Serious gastrointestinal side effects (affecting the stomach and intestines) have been reported with the use of NSAIDs, including ibuprofen. These can occur with or without warning symptoms. The risk of these side effects is higher in patients with a history of ulcers of the stomach or intestines, particularly if bleeding or perforation was also involved. Elderly patients are at greater risk of gastrointestinal side effects. You should discuss any history of gastrointestinal problems with your doctor, and remain alert for any unusual abdominal symptoms, including nausea, vomiting, diarrhoea, constipation, indigestion, abdominal pain, tar-like stools, or vomiting blood.

Elderly patients should first discuss treatment with a doctor. Elderly patients are at greater risk of side effects, especially bleeding and perforation in the digestive tract.

Skin reactions
Serious skin reactions have been reported in association with ibuprofen treatment. You should tell your doctor or nurse immediately if you develop any skin rash, lesions of the mucous membranes, blisters or other signs of allergy since these can be the first signs of a very serious skin reaction. See section 4.

Infections
Combogesic may hide signs of infections such as fever and pain. It is therefore possible that Combogesic may delay appropriate treatment of infection, which may lead to an increased risk of complications. This has been observed in pneumonia caused by bacteria and bacterial skin infections related to chickenpox. If you are given this medicine while you have an infection and your symptoms of the infection persist or worsen, consult a doctor without delay.

Prolonged use of painkillers
If you use painkillers for a long time, this can cause headaches, which should not be treated with more painkillers. If you think this applies to you, talk to your doctor or pharmacist.

Vision problems
If you notice any problems with your vision after using Combogesic stop using the medicine and see a doctor.

Children and adolescents

Combogesic is not for use in children and adolescents under 18 years.

Other medicines and Combogesic

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

Always tell the doctor if you are taking other medicines containing paracetamol, ibuprofen or other NSAID painkillers, including those you can buy without a prescription. This is to avoid the risk of overdose.

Combogesic may affect or be affected by some other medicines. For example:
- acetylsalicylic acid, salicylates or other NSAID medicines (including COX-2 inhibitors such as celecoxib or etoricoxib);
- medicines to treat heart conditions (e.g. digoxin or beta blockers);

- corticosteroids, such as prednisone, cortisone;
- medicines that are anti-coagulants (i.e. thin blood/prevent clotting e.g. acetylsalicylic acid, warfarin, ticlopidine);
- medicines that reduce high blood pressure (ACE-inhibitors such as captopril, beta-blockers such as atenolol, angiotensin-II receptor antagonists such as losartan);
- medicines to treat epilepsy or fits (e.g. phenytoin, phenobarbital, carbamazepine);
- medicines used to treat mania (e.g. lithium);
- medicines used to treat depression e.g. SSRIs (selective serotonin-reuptake inhibitors);
- probenecid, a medicine used to treat gout;
- diuretics, medicines used to increase urine output;
- methotrexate, a medicine used to treat arthritis and some types of cancer;
- tacrolimus or ciclosporin, immunosuppressive drugs used after organ transplant;
- zidovudine, a medicine used to treat HIV (the virus that causes AIDS);
- sulphonylureas, a medicine used to treat diabetes;
- a type of antibiotic known as quinolone antibiotics (e.g. ciprofloxacin);
- a type of antibiotic known as aminoglycosides (e.g. gentamicin, streptomycin);
- chloramphenicol, an antibiotic used to treat ear and eye infections;
- antifungal medicines such as voriconazole or fluconazole;
- medicines used to treat tuberculosis such as isoniazid and rifampicin;
- mifepristone, a medicine used for medical termination of a pregnancy;
- some herbal remedies, such as ginkgo biloba (sometimes used for dementia), or St John's wort (*Hypericum*, sometimes used for mild depression).
- flucloxacillin (antibiotic), due to a serious risk of blood and fluid abnormality (high anion gap metabolic acidosis) that must have urgent treatment and which may occur particularly in case of severe renal impairment, sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), malnutrition, chronic alcoholism, and if the maximum daily doses of paracetamol are used.

Some other medicines may also affect or be affected by the treatment of Combogesic. You should therefore always seek the advice of your doctor, nurse or pharmacist before you take any other medicines.

If you need to leave a blood or urine sample for analysis, you need to tell your doctor that you are taking this medicine as it may interfere with the test results.

Combogesic with alcohol
Do not drink alcoholic beverages when treated with this medicine. Combining alcohol with Combogesic may lead to liver damage.

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 nurse for advice before this medicine is given to you.

Pregnancy
Do not take Combogesic if you are in the last 3 months of pregnancyas it could harm your unborn child or cause problems at delivery. It can cause kidney and heart problems in your unborn baby. It may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected. You should not take Combogesic during the first 6 months of pregnancy unless absolutely

necessary and advised by your doctor. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used. If taken for more than a few days from 20 weeks of pregnancy onward, Combogesic can cause kidney problems in your unborn baby that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios) or narrowing of a blood vessel (ductus arteriosus) in the heart of the baby. If you need treatment for longer than a few days, your doctor may recommend additional monitoring.

Breast-feeding
Only small amounts of paracetamol and ibuprofen pass into breast milk. This medicine may be given during breast-feeding, if it is used at the recommended dose and for the shortest possible time.

Fertility
This product may impair female fertility and is not recommended in women attempting to conceive. This effect is reversible on stopping the medicine.

Driving and using machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected you should not drive or operate machinery.

Combogesic contains sodium

Combogesic contains 35 mg (1.52 mmol) sodium (main component of cooking/table salt) in each 100 ml (0.35 mg (0.0152 mmol) per 1 ml). This is equivalent to 1.75% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Combogesic

Combogesic will be given to you by a healthcare professional by infusion into one of your veins. The infusion should be administered over 15 minutes.

This medicine is for short term use only, maximum 2 days.

The recommended dose is:
For adults who weigh more than 50 kg: 1 vial every 6 hours, as required.

The maximum daily dose is four vials which equals 4000 mg (400 ml) paracetamol and 1200 mg (400 ml) ibuprofen.

If you weigh 50 kg or less, are elderly or if you have liver or kidney problems: Your doctor may decide to reduce your dose or increase the time between doses because of the increased risk of side effects.

A higher dose than the recommended does not increase pain relief; instead it can lead to serious risks (see also section "**If you are given more Combogesic than you should**"). The lowest effective dose should be given for the shortest duration necessary to relieve symptoms. If you have an infection, consult a doctor without delay if symptoms (such as fever and pain) persist or worsen (see section 2).

If you are given more Combogesic than you should

Immediately contact a doctor or nurse if you think that you accidentally may have been given too much of this medicine. **Do this even if you feel well**. This is because too much paracetamol can cause delayed, serious liver damage, which may be fatal. Even if there are no signs of discomfort or poisoning, you may need urgent medical attention.

In order to avoid liver damage, it is essential to get medical treatment as early as possible. The shorter the interval between intake and initiation of treatment with antidote (as few hours as possible), the greater the likelihood that hepatic injury can be prevented.

Further symptoms can include nausea, stomach pain, vomiting (may be blood streaked), headache, ringing in the ears, confusion and shaky eye movement. At high doses, drowsiness, chest pain, palpitations, loss of consciousness, convulsions (mainly in children), weakness and dizziness, blood in urine, cold body feeling, and breathing problems have been reported.

4. Possible side effects

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

Stop using Combogesic and tell your doctor **immediately** or go to the emergency room at your nearest hospital if you get any of the following side effects:

Uncommon:
- vomiting blood or material that looks like coffee grounds;
- bleeding from the back passage, black sticky bowel motions (stools) or bloody diarrhoea;
- swelling of the face, lips or tongue which may cause difficulty in swallowing or breathing.

Very rare:
- asthma, wheezing, shortness of breath;
- sudden or severe itching, skin rash, hives;
- severe rash with blisters and bleeding in the lips, eyes, mouth, nose and genitals (Steven Johnson Syndrome). Very rare cases of serious skin reactions have been reported;
- worsening of existing severe skin infections (you may notice a rash, blistering and discolouration of the skin, fever, drowsiness, diarrhoea and sickness), or worsening of other infections including chicken pox or shingles or severe infection with destruction (necrosis) of subcutaneous tissue and muscle, blistering and peeling of the skin;
- fever, generally feeling unwell, nausea, stomach ache, headache and stiff neck (symptoms of aseptic meningitis, inflammation of the protective membrane surrounding the brain).

Not known (frequency cannot be estimated from the available data):
- a severe skin reaction known as DRESS syndrome can occur. Symptoms of DRESS include: skin rash, fever, swelling of lymph nodes and an increase of eosinophils (a type of white blood cells).
- a red, scaly widespread rash with bumps under the skin and blisters mainly localised on the skin folds, trunk, and upper extremities accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis). See also section 2.

Other side effects that may occur:

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

- nausea or vomiting;
- loss of appetite;
- heartburn or pain the upper part of your stomach;
- stomach cramps, wind, constipation or diarrhoea, slight gastrointestinal blood loss;
- skin rashes, itching of the skin;
- headache;
- dizziness;
- feeling of being nervous;
- ringing or buzzing in the ears;
- unusual weight gain, swelling and fluid retention, swelling of ankles or legs (oedema).

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

- decrease in red blood cells, nose bleed and heavier periods (menstrual bleeding);
- allergic reactions – skin rash, tiredness, joint pain (e.g. serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis, angioedema);
- enlargement of breast tissue in men; low blood sugar levels;
- sleeplessness;
- change in mood, for example depression, confusion, nervousness;
- eye problems such as blurred vision (reversible), sore red eyes, itching;
- thickened mucus;
- severe pain or tenderness in the stomach; peptic/gastrointestinal ulcer;
- Bowel inflammation and worsening of inflammation of the colon (colitis) and digestive tract (Crohn's disease) and complications of diverticula of the large bowel (perforation or fistula);
- inability to completely empty the bladder (urinary retention);
- abnormal laboratory test results (blood, liver and kidney enzyme test results).

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

- tingling of the hands and feet;
- abnormal dreams, seeing things (hallucinations);
- damage of the kidney tissue (particularly in long-term use);
- high level of uric acid in your blood (hyperuricemia).

Very rare (may affect up to 1 in 10,000 people):

- low potassium levels – weakness, fatigue, muscle cramps (hypokalaemia);
- signs of anaemia, such as tiredness, headaches, being short of breath, and looking pale;
- bleeding or bruising more easily than normal, reddish or purplish blotches under the skin;
- severe or persistent headache;
- spinning sensation (vertigo);
- fast or irregular heartbeats, also called palpitations;
- increase in blood pressure and possible heart problems;
- inflammation of the oesophagus;
- yellowing of the skin and /or eyes, also called jaundice;
- liver damage (particularly in long term use);
- loss of hair;

- increase in sweating;
- signs of frequent or worrying infections such as fever, severe chills, sore throat or mouth ulcers;
- nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure.

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 the national reporting system:

HPRA Pharmacovigilance
Website: www.hpra.ie
By reporting side affects you can help provide more information on the safety of this medicine.

5. How to store Combogesic

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

Store below 25°C. Do not refrigerate or freeze. Store in the original carton in order to protect from light.

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

Do not use this medicine if you notice the packaging is torn or shows signs of tampering. Do not use this medicine if you notice any visible particles or discolouration.

This product is for single use only. The product should be used immediately after opening. Any unused solution should be discarded.

Dispose in accordance with local requirements.

6. Contents of the pack and other information

What Combogesic contains

The active substances are 10 mg/ml paracetamol and 3 mg/ml ibuprofen (as sodium dihydrate).

The other ingredients are cysteine hydrochloride monohydrate, disodium phosphate dihydrate, mannitol (E421), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injections.

What Combogesic looks like and contents of the pack

Combogesic is a clear, colourless solution for infusion, free from visible particles. It is supplied in 100 ml clear glass vials, closed with a grey bromobutyl rubber stopper and an aluminium flip-off cap. It comes in a pack size of 10 vials.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:

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PA23183/002/001

Manufacturer:

S.M. Farmaceutici SRL
Zona Industriale
85050 Tito (PZ)
Italy

This medicine is authorised in the Member States of the European Economic Area under the following names:

Name of the Member State	**Name of the medicine**
Greece	Combogesic
Ireland	Combogesic 10mg/ml Paracetamol + 3mg/ml Ibuprofen solution for infusion
Portugal	Combogesic IV
Sweden	Duofen

This leaflet was last revised

The following information is intended for healthcare professionals only:

Combogesic 10 mg/ml Paracetamol + 3 mg/ml Ibuprofen solution for Infusion

Visually inspect Combogesic for particulate matter and discolouration prior to administration, whenever solution and container permit. If visibly opaque particles, discolouration or other foreign particulates are observed, the solution should not be used.

In the absence of compatibility studies, this medicine should not be mixed with diluents. If less than a full vial is required for a single dose, the correct amount should be infused and the remaining solution discarded.

Combogesic should be used in one patient on one occasion only. It contains no antimicrobial preservative. Any unused solution should be discarded.

Method of administration
Combogesic 10mg/ml Paracetamol + 3mg/ml Ibuprofen solution for infusion should be administered as a 15-minute intravenous infusion.

To remove solution, use a 0.8 mm needle (21 gauge needle) and vertically perforate the stopper at the spot specifically indicated.

In patients weighing less than 50 kg for whom a full vial (100 ml) is not required, the correct amount should be infused and the remaining solution discarded.

As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the perfusion applies particularly for central route infusion, in order to avoid air embolism.