B. PACKAGE LEAFLET

Package leaflet: information for the user

Irinotecan 1.5 mg/ml solution for infusion

irinotecan hydrochloride trihydrate

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.
- 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 Irinotecan is and what it is used for

Irinotecan is an anticancer medicine containing the active substance irinotecan hydrochloride, trihydrate.

Irinotecan hydrochloride trihydrate interferes with the growth and spread of cancer cells in the body.

Irinotecan is indicated in combination with other medicines for the treatment of patients with advanced or metastatic cancer of the colon or rectum.

Irinotecan may be used alone in patients with metastatic cancer of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

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

You should NOT be given Irinotecan if any of the following apply to you. Tell your doctor if
- you have chronic inflammatory bowel disease and/or bowel obstruction
- you are allergic to irinotecan hydrochloride trihydrate or any of the other ingredients of this medicine (listed in section 6)
- you are breastfeeding (see section 2)
- you have increased levels of bilirubin in the blood (more than 3 times the upper limit of the normal range)
- you have severe bone marrow failure
- your general health does not allow you to carry out normal activities of daily living (WHO performance status higher than 2)
- you are taking or have recently taken St John's Wort (a herbal extract containing Hypericum)
- you are to take or have recently taken live attenuated vaccines (vaccines against yellow fever, chicken pox, shingles, measles, mumps, rubella, tuberculosis, rotavirus, influenza) and during the 6 months after stopping chemotherapy.

If you receive Irinotecan in combination with other medicines, please make sure that you also read the package leaflet of the other medicines regarding additional contraindications.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Irinotecan
- if you have Gilbert's syndrome, an inherited condition that can cause elevated bilirubin levels and jaundice (yellow skin and eyes).

As Irinotecan is an anti-cancer medicine it will be given to you in a special unit and under supervision of a doctor qualified in the use of anti-cancer medicines. The units' staff will explain to you what special care you need to take during and after the treatment. This leaflet may help you to remember that.

Children
This medicine is intended for adults only. Check with your doctor if this medicine has been prescribed for use in a child.

Elderly patients
Special care is needed in elderly patients.

Diarrhoea
Irinotecan can cause diarrhoea, which in some cases may be severe. This may start a few hours or a couple of days after the medicine infusion. If left untreated, it could lead to dehydration and serious chemical imbalances, which can be life threatening. Your doctor will prescribe medicine to help prevent or control this side effect. Make sure you get the medicine right away, so that you will have it at home when you need it.
- take the medicine as prescribed at the first sign of loose or frequent bowel movements
- drink large amounts of water and (or) salty drinks (fizzy water, soda or soup)
- call your doctor or nurse to know if you still have diarrhoea, especially if it lasts more than 24 hours, or if you get lightheaded, dizzy, or faint.

Neutropenia (decrease in some white blood cells)
This medicine can lower your white blood cell count, mainly in the weeks after the medicine is given. This can increase the risk of getting an infection. Be sure to let your doctor or nurse know right away if you have any signs of infection, such as fever (38°C or higher), chills, pain when passing urine, a new cough, or bringing up sputum. Avoid being near people who are sick or have infections. Tell your doctor at once if you develop signs of infection.

Blood monitoring
Your doctor will likely test your blood before and during your treatment, to check for effects of the medicine on blood counts or on blood chemistry. Based on the test results, you may need medicines to help treat the effects. Your doctor may also need to reduce or delay your next dose of this medicine, or even stop it altogether. Keep all your appointments for doctor visits and lab tests.

This medicine may lower your platelet count in the weeks after it is given, which can increase your risk of bleeding. Speak with your doctor before taking any medicine or supplement that might affect your body's ability to stop bleeding, such as aspirin or aspirin-containing medicines, warfarin, or vitamin E. Tell your doctor right away if you have unusual bruising, or bleeding such as nosebleeds, bleeding gums when you brush your teeth, or black, tarry stools.

Nausea and vomiting
You may have nausea and vomiting on the day you receive this medicine or in the first few days after. Your doctor may give you medicine before your treatment to help prevent nausea and vomiting. Your doctor will likely prescribe anti-nausea medicines that you can take at home. Have these medicines on

hand for when you need them. Call your doctor if you are unable to take fluids by mouth due to nausea and vomiting.

Acute cholinergic syndrome
This medicine may affect part of your nervous system that controls body secretions, leading to what is known as cholinergic syndrome. Symptoms can include runny nose, increased saliva, excess tears in the eyes, sweating, flushing, abdominal cramps, and diarrhoea. Let your doctor or nurse know right away if you notice any of these symptoms, as there are medicines that can help control them.

Lung disorders
Rarely, people on this medicine have serious lung problems, Tell your doctor right away if you have new or worsening cough, trouble breathing, and fever. Your doctor may need to stop your treatment to manage this problem.
This medicine may increase your risk of major blood clots in the veins of the legs or lungs, which can travel to other parts of the body such as the lungs or brain. Tell your doctor right away if you notice chest pain, shortness of breath, or swelling, pain, redness, or warmth in an arm or leg.

Chronic intestinal inflammation and/or intestinal blockage
Call your doctor if you have pain in your belly and you cannot move your bowels, especially if you also have bloating and loss of appetite.

Irradiation therapy
If you recently received treatment with pelvic or abdominal radiotherapy, you may be at increased risk of developing bone marrow suppression. Please talk to your doctor before starting with Irinotecan.

Kidney function
Occurrences of kidney dysfunction have been reported.

Cardiac disorders
Inform your doctor if you suffer/suffered from heart disease or if you previously received anti-cancer medicines. Your doctor will monitor you closely and discuss with you how risk factors (for example smoking, high blood pressure and to high fat content) can be reduced.

Vascular disorders
Irinotecan is rarely associated with blood flow disorders (blood clots in the vessels of your legs and lungs) and it may occur rarely in patients with multiple risks factors.

Others
This medicine may cause sores in the mouth or on the lips, often within the first few weeks after starting treatment. This can cause mouth pain, bleeding, or even trouble eating. Your doctor or nurse can suggest ways to reduce this, such as changing the way you eat or how you brush your teeth. If needed, your doctor can prescribe medicine to help with the pain.

For contraception and breast-feeding information, refer to the information provided below under section Contraception, pregnancy, breast-feeding and fertility.

Tell your doctor or dentist that you are on this medicine if you are planning to have surgery or any procedure.

If used in combination with other anticancer medicines for your condition please make sure that you also read the leaflets for the other medicine.

Other medicines and Irinotecan

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

Irinotecan can interact with a number of medicines and supplements, which may either raise or lower the level of the medicine in your blood.

Tell your doctor if you are taking any of the following medicines
- medicines used to treat seizure (carbamazepine, phenobarbital, phenytoin and fosphenytoin)
- medicines used to treat fungal infection (ketoconazole, itraconazole, voriconazole and posaconazole)
- medicines used to treat bacterial infection (clarithromycine, erythromycin and telithromycine)
- medicines used to treat tuberculosis (rifampicin and rifabutin)
- St John's Wort (a herbal dietary supplement)
- live attenuated vaccines
- medicines used to treat HIV (indinavir, ritonavir, amprenavir, fosamprenavir, nelfinavir, atazanavir, and others)
- medicines used to suppress your body's immune system to prevent transplant rejection (ciclosporin or tacrolimus)
- medicines used to treat cancer (regorafenib, crizotinib, idelalisib and apalutamide)
- vitamin K antagonists (an anticoagulant used to thin the blood such as warfarin)
- medicines used to relax muscles used during general anaesthesia and surgery (suxamethonium)
- 5-fluorouracil/folinic acid
- bevacizumab (a blood vessel growth inhibitor)
- cetuximab (an EGF receptor inhibitor).

Tell your doctor pharmacist or nurse before being given Irinotecan if you are already having, or have recently had chemotherapy (and radiotherapy).

Don't start or stop taking any medicines while you are on Irinotecan without talking with your doctor first.

This medicine can cause serious diarrhoea. Try to avoid laxatives and stool softeners while taking this medicine.

There may be more medicines that interact with Irinotecan. Check with your doctor, pharmacist or nurse about your other medicines, herbs, and supplements, and whether alcohol can cause problems with this medicine.

Contraception, pregnancy, breast-feeding and fertility
Contraception
If you are a woman of childbearing potential, then you have to use effective contraception during and up to 6 months after stopping treatment.

As a man, you have to use effective contraception during and up to 3 months after stopping treatment. It is important to check with your doctor about what kinds of birth control can be used with this medicine.

Pregnancy
This medicine may cause problems with the foetus if taken at the time of conception or during pregnancy. Before initiating treatment, your doctor will ensure that you are not pregnant.

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

Breast-feeding
Irinotecan and its metabolite were measured in human milk. Breast-feeding should be discontinued for the duration of your treatment with this medicine.

If you are breast-feeding ask your doctor or pharmacist for advice before taking this medicine.

Fertility
No studies have been done, nevertheless, this medicine may affect fertility. Talk with your doctor about the possible risk with this medicine and the options that may preserve your ability to have children.

Driving and using machines
In some cases Irinotecan may cause side effects which affect the ability to drive and use tools and machines. Contact your doctor or pharmacist if you are unsure.

During the first 24 hours after administration of Irinotecan you may feel dizzy or have visual disturbances. If this happens to you, do not drive or operate machinery until this resolves.

Irinotecan contains sorbitol
This medicine contains a sugar (sorbitol).
This medicine contains 607.50 mg sorbitol in each 180 ml infusion bag which is equivalent to 3.375 mg/ml.
This medicine contains 675.00 mg sorbitol in each 200 ml infusion bag which is equivalent to 3.375 mg/ml.
This medicine contains 742.50 mg sorbitol in each 220 ml infusion bag which is equivalent to 3.375 mg/ml.
This medicine contains 810.00 mg sorbitol in each 240 ml infusion bag which is equivalent to 3.375 mg/ml.
Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.
You must tell your doctor before receiving this medicine if you have HFI.

Irinotecan contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

Irinotecan contains glucose
This medicine contains 8.325 g glucose in each 180 ml infusion bag.
This medicine contains 9.250 g glucose in each 200 ml infusion bag.
This medicine contains 10.175 g glucose in each 220 ml infusion bag.
This medicine contains 11.100 g glucose in each 240 ml infusion bag.
This should be taken into account in patients with diabetes mellitus.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How Irinotecan will be given

If you are prescribed Irinotecan it will only be given to you by doctors or nurses experienced in giving chemotherapy.

Method of administration
Irinotecan will be given as an infusion (drip) into your veins over a period of 30 to 90 minutes.

You may be given other medications to prevent nausea, vomiting, diarrhoea, and other side effects while you are receiving Irinotecan. You may need to keep using these medicines for at least a day after your Irinotecan infusion.

Tell your care givers if you feel any burning, pain, or swelling around the IV needle when Irinotecan is administered. If the medicine escapes from the vein it can cause tissue damage. If you experience pain or notice redness or swelling at the IV site while you are receiving Irinotecan, alert your healthcare professional immediately.

How much Irinotecan is given
The dose will depend on a number of factors, including the treatment schedule, your body size, your age and general health, your blood counts, how well your liver is working, whether you have had radiation to your abdomen/pelvis, and whether you have any side effects such as diarrhoea. Your doctor will calculate your body surface area in square meters (m^2).
- if you have previously been treated with 5-fluorouracil you will normally be treated with Irinotecan alone starting with a dose of 350 mg/m^2 every three weeks
- if you have not had previous chemotherapy you will normally receive 180 mg/m^2 Irinotecan every two weeks. This will be followed by folinic acid and 5-fluorouracil.

If you receive Irinotecan in combination with cetuximab, Irinotecan must not be administered earlier than 1 hour after the end of the cetuximab infusion.

Only your doctor may assess the duration of treatment.

The number of infusions that you receive will depend on how you are responding to treatment. Your doctor will discuss this with you.

If you are given more Irinotecan than you should
Seek emergency medical attention if you think that you have been given too much Irinotecan. An overdose worsens side effects like diarrhoea or neutropenia (a decrease in the number of white blood cells in the blood). Should this happen, you will receive treatment to prevent dehydration. Your blood cell count will be monitored and any infections treated accordingly.

If you forget to use Irinotecan
Call your doctor for instructions if you miss an appointment for your Irinotecan infusion.
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. Your doctor will discuss these side effects with you and explain the risks and benefits of your treatment.

Some side effect could be serious. You must immediately contact your doctor if you experience any of those following serious side effects (see section 2).
Get emergency medical help if you have any of these signs of an allergic reaction: hives; difficult breathing; swelling of your face, lips, tongue, or throat.

- diarrhoea (see section 2).
- early diarrhoea: Occurring within 24 hours of receiving this medicine, accompanied by symptoms runny nose, increased salivation, watery eyes, sweating, flushing, abdominal cramping. (This can occur while the medicine is being administered. If so, alert your healthcare professional promptly. Medication can be given to stop and/or lessen this early side effect).

- late diarrhoea: Occurring greater than 24 hours of receiving this medicine. Because of concerns of dehydration and electrolyte imbalances with diarrhoea it is important to be in contact with health care professionals for monitoring, and for medication and diet modifications advice.

Talk to your doctor or nurse if you experience any of the symptoms below

Symptoms	**Frequency* of occurrence in Monotherapy**	**Frequency† of occurrence in Combination Therapy**
Abnormally low number of white blood cells which could put you at increased risk for infection	Very common	Very common
Low number of red blood cells causing tiredness and shortness of breath	Very common	Very common
Decreased appetite	Very common	Very common
Cholinergic syndrome (see section 2"Warnings and Precautions")	Very common	Very common
Vomiting	Very common	Very common
Nausea	Very common	Very common
Abdominal pain	Very common	Common
Hair loss (reversible)	Very common	Very common
Inflammation of mucous membranes	Very common	Very common
Fever	Very common	Common
Feeling weak and having no energy	Very common	Very common
Low number of platelets (blood cells that help with clotting) which may cause bruising or bleeding	Common	Very common
Abnormal liver function test values	Common	Very common
Infection	Common	Common
Low number of white blood cells with fever	Common	Common
Difficulty in passing stools	Common	Common
Abnormal kidney function test values	Common	Not reported

* Very common: may affect more than 1 in 10 people
† Common: may affect up to 1 in 10 people

Not known: frequency cannot be estimated from the available data
- severe, persistent or bloody diarrhoea (which may be associated with stomach pain or fever) caused by bacteria called (*Clostridium difficile*)

- blood infection
- dehydration (due to diarrhoea and vomiting)
- dizziness, rapid heartbeat and pale skin (a condition called hypovolaemia)
- allergic reaction
- temporary speech disorders during or shortly after treatment
- pins and needles
- high blood pressure (during or after infusion)
- heart problems*
- lung disease causing wheezing and shortness of breath (see section 2)
- hiccups
- intestinal blockage
- enlarged colon
- bleeding from the bowels
- inflammation of the large intestine
- abnormal lab test results
- hole in the intestine
- fatty liver disease
- skin reactions
- reactions at the site where the medicine was administered
- low level of potassium in the blood
- low level of salt in the blood mostly related with diarrhoea and vomiting
- muscle cramps
- kidney problems*
- low blood pressure*
- fungal infections
- viral infections.

* Infrequent cases of these events have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or infections of the blood.

If you receive Irinotecan in combination with cetuximab, some of the side effects that you may experience can also be related to this combination. Such side effects may include an acne- like rash. Therefore, please make sure that you also read the package leaflet for cetuximab.

If you receive Irinotecan in combination with capecitabine, some of the side effects that you may experience can also be related to this combination. Such side effects may include: very common blood clots, common allergic reactions, heart attack and fever in patients with a low white blood cell count. Therefore, please make sure that you also read the package leaflet for capecitabine.

If you receive Irinotecan in combination with capecitabine and bevacizumab, some of the side effects that you may experience can also be related to this combination. Such side effects include: low white blood cell count, blood clots, high blood pressure and heart attack. Therefore, please make sure that you also read the package leaflet for capecitabine and bevacizumab.

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 via the Yellow Card Scheme at 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 Irinotecan

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 infusion bag and the outer packaging after EXP. The expiry date refers to the last day of that month.

Store below 25°C. Store in the original package in order to protect from light.

After opening, the infusion bag should be used immediately.

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 Irinotecan contains
- The active substance is irinotecan (as hydrochloride trihydrate).
- The other ingredients are: glucose (E620), sorbitol (E420), (S)-lactic acid (E270), sodium hydroxide (for pH adjustment) (E524), hydrochloric acid, concentrated (for pH adjustment) (E507) and water.

One 180 ml infusion bag contains 270 mg irinotecan hydrochloride trihydrate (corresponding to 234 mg irinotecan).
One 200 ml infusion bag contains 300 mg irinotecan hydrochloride trihydrate (corresponding to 260 mg irinotecan).
One 220 ml infusion bag contains 330 mg irinotecan hydrochloride trihydrate (corresponding to 286 mg irinotecan).
One 240 ml infusion bag contains 360 mg irinotecan hydrochloride trihydrate (corresponding to 312 mg irinotecan).

One ml of the solution for infusion contains 1.5 mg irinotecan hydrochloride trihydrate (corresponding to 1.3 mg/ml irinotecan).

What Irinotecan looks like and contents of the pack
Irinotecan solution for infusion is a clear, pale yellow to yellow, sterile solution free from visible particulate matter.
Irinotecan solution for infusion is supplied in carton boxes each containing 1, 5 or 10 single dose infusion bags of 180 ml, 200 ml, 220 ml or 240 ml.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Sun Pharmaceutical Industries Europe BV
Polarisavenue 87
2132 JH Hoofddorp
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Manufacturer
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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

Germany:	Irinotecan SUN
Denmark:	Irinotecan SUN
Spain:	Irinotecán SUN
Finland:	Irinotecan SUN
France:	Irinotecan SUN
Italy:	Irinotecan SUN
Romania:	Irinotecan SUN
Sweden:	Irinotecan SUN
United Kingdom (Northern Ireland):	Irinotecan

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The following information is intended for healthcare professionals only

Handling
- calculate the dose, and decide which size of the Irinotecan infusion bags is needed
- inspect the product pack for any damage. Do not use if there are signs of tampering
- apply patient-specific label on the overwrap

Removal of infusion bag from overwrap and infusion bag inspection
- tear overwrap at notch. Do not use if overwrap has been previously opened or damaged
- remove infusion bag from overwrap
- use only if infusion bag and seal are intact. Prior to administration check for minute leaks by squeezing bag firmly. If leaks are found, discard the bag and solution as sterility may be impaired
- parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter and discoloration is observed, do not administer

Administration
- break the stopper seal by applying pressure on one side with hand
- using aseptic technique, attach sterile administration set
- refer to directions for use accompanying the administration set

Precautions
- do not use in series connection
- do not introduce additives into the infusion bag
- the solution for infusion is ready to use and must not be mixed with other medicinal products
- Irinotecan solution for infusion is for single use only.

Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area and collection bags for waste.

Cytotoxic preparations should not be handled by pregnant staff.

If the product comes into contact with the eyes, severe irritation may result. In such an event, the eyes should be washed thoroughly and immediately. Consult a doctor if irritation persists. If the solution should come into contact with skin, rinse the affected area thoroughly with water. Excreta and vomit must be handled with care.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.