PACKAGE LEAFLET: INFORMATION FOR THE USER

Irinotecan 20 mg/ml

Concentrate for solution for infusion

irinotecan hydrochloride, trihydrate

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.

What is in this leaflet

1. WHAT IRINOTECAN IS AND WHAT IT IS USED FOR

This medicinal product belongs to a group of medicines called antineoplastic cytostatics (anti-cancer medicines). Irinotecan is indicated for the treatment of adult patients with advanced colorectal cancer, either combined with other medicines or as a single agent.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE IRINOTECAN

Do not take Irinotecan:
- if you are allergic to irinotecan hydrochloride trihydrate or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from chronic inflammatory bowel disease and/or bowel obstruction
- if you are breast feeding
- if you have liver problems with increased bilirubin values in your blood (more than 3 times higher than the upper limit of the normal range)
- if you have an imbalance of your blood cells (severe bone marrow failure)
- if you are in poor general health (WHO performance status greater than 2)
- if you are taking any prescription medicines or herbal extract containing St John's Wort (medicine against depression).

If you receive Irinotecan in combination with 5-fluorouracil, capecitabine, cetuximab or bevacizumab, please make sure that you also read the package inserts of these medicinal products.

Warnings and precautions
Talk to you doctor or pharmacist before taking Irinotecan.

Irinotecan will be given to you only in units specialised in the administration of anti-cancer medicines (antineoplastic cytotoxic chemotherapy), under the supervision of a physician qualified in the use of these medicines. The unit's personnel will explain to you what you need to take special care of during and after the treatment. This leaflet may help you to remember that.

This medicine is intended for adults only.

Check with your doctor if this medicine has been prescribed for use in a child.
Special care is also needed in elderly patients.

During administration of Irinotecan (30-90 min.) and up to 24 hours after administration you may experience some of the following symptoms: diarrhoea, sweating, abdominal pain, visual disturbance, excessive mouth watering. The medical term for these symptoms is "acute cholinergic syndrome" which can be treated (with atropine). If you have any of these symptoms immediately tell your doctor who will give you any treatment necessary.

From the day after treatment with Irinotecan until next treatment you may experience various symptoms, which may be serious and require immediate treatment and close supervision.

Diarrhoea
If your diarrhoea starts more than 24 hours after administration of This medicine ("delayed diarrhoea") it may be serious. It is often seen about 5 days after administration. The diarrhoea should be treated immediately and kept under close supervision. Immediately after the first liquid stools do the following:

- Take any anti-diarrhoeal treatment that the doctor has given you, exactly as he/she has told you. The treatment may not be changed without consulting the doctor. Recommended anti-diarrhoeal treatment is loperamide (4 mg for the first intake and then 2 mg every 2 hours, also during the night). This should be continued for at least 12 hours after the last liquid stools. The recommended dosage of loperamide may not be taken for more than 48 hours.
- Drink large amounts of water and rehydration fluids, immediately (i.e. water, soda water, fizzy drinks, soup or oral rehydration therapy).
- Immediately inform your doctor who is supervising the treatment, and tell him/her about the diarrhoea. If you are not able to reach the doctor, contact the unit at the hospital supervising the Irinotecan treatment. It is very important that they are aware of the diarrhoea.

Hospitalisation is recommended for the management of the diarrhoea, in the following cases:
- you have diarrhoea as well as fever (over 38°C)
- you have severe diarrhoea (and vomiting) with excessive loss of water requiring intravenous hydration
- you still have diarrhoea 48 hours after starting the diarrhoea treatment

Note! Do not take any treatment for diarrhoea other than that given to you by your doctor and the fluids described above. Follow the doctors instructions. The anti-diarrhoeal treatment should **not** be used preventatively, even though you have experienced delayed diarrhoea at previous cycles.

Blood monitoring
Irinotecan may cause a decrease in the number of some of your white blood cells, which play an important role in fighting infections. This is called neutropenia. Neutropenia is often seen during treatment with irinotecan and is reversible. Your doctor should arrange for you to have regular blood tests to monitor these white blood cells. Neutropenia is serious and should be treated immediately and carefully monitored.

Fever
If you have any fever over 38°C contact your doctor or the unit immediately so that they can give you any treatment necessary.

Breathing difficulties
If you have any breathing difficulties contact your doctor immediately.

Impaired liver function
Before treatment with Irinotecan is started and before every following treatment cycle your doctor will monitor your liver function (by blood tests).

Nausea (feeling sick) and vomiting
If you have nausea and/or vomiting contact your doc tor or the hospital unit immediately.

Impaired kidney function
As this medicine has not been tested in patients with kidney problems, please check with your doctor if you have any kidney problems.

Cardiac disorders
If you have heart problems or additional risk factors such as smoking, high blood pressure or high cholesterol your doctor will monitor your condition.

Increase susceptibility to infections
Chemotherapeutic agents may damper down your body's immune systems. Special care should be taken with the administration of live or live-atenuated vaccines. Vaccination with a live vaccine should be avoided.

Alterations in the composition of your blood
Due the the risk of alterations in the composition of your blood, your doctor will monitor your blood at weekly intervals."

Dehydration
Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Other medicines and Irinotecan:
Please inform your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following medicines may change Irinotecan effects, and therefore should not be administered concomitantly:
- Carbamazepine, phenobarbital or phenytoin (drugs used in the management of epilepsy);
- Ketoconazole (used for the treatment of fungal infections);
- Rifampicin (used for the treatment of tubercolosis);
- Warfarin (an anticoagulant used to thin the blood);
- Atazanavir (used to treat HIV);
- Vaccines (response to killed or inactivated vaccines may be diminished);
- Ciclosporin or Tacrolimus (used to dampen down your body's immune system).

Natural medicines based on St John's Wort (*Hypericum perforatum*) must not be co-administered with this medicine, not even between treatments, since it can affect Irinotecan efficacy. If you are taking any preparations containing St John's Wort, please suspend it immediately and inform your doctor.

The following medicines may be influenced by Irinotecan:
- Muscle relaxants used during surgery (e.g. suxamethonium, non-depolarising drugs), as Irinotecan may prolong or block their effects. If you require an operation, please tell your doctor or anaesthetist that you are using this medicine.

Irinotecan with food and drink - Not applicable.

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

Pregnancy
You must not receive this medicine if you are pregnant unless clearly indicated.

If you are in child-bearing age and receiving Irinotecan treatment, you should be advised to avoid becoming pregnant. Contraceptive measures must be taken by both male and female patients during treatment and until 3 months after the end of treatment.
Still, if you become pregnant during this period you must immediately inform your doctor.

Breast-feeding
It is not known whether Irinotecan is excreted in human milk. Consequently, you must not breast-feed while you are treated with this product.

Driving and using machines
Due to the potential for dizziness or visual disturbances, which may occur within 24 hours following administration of Irinotecan, you should not drive or operate machinery if these symptoms occur.
Contact your doctor or pharmacist in case of any doubt.

Irinotecan contains sorbitol.
This medicine contains 45 mg sorbitol in each millilitre of solution.
Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) 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 (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

This medicine contains less than 1 mmol sodium (23 mg) per mL of solution, that is to say essentially 'sodium-free'

3. HOW TO TAKE IRINOTECAN

This medicinal product will be administered as an intravenous infusion over a 30 to 90 minute period. Dosage will depend on your age, size and general clinical condition. It will also depend on any other treatment you may have received for your cancer. Your doctor will calculate your body surface 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 350mg/m^2 every 3 weeks.
- If you have not had previous chemotherapy you will normally receive 180mg/m^2 of Irinotecan every 2 weeks. This will be followed by folinic acid and 5-fluorouracil administration.

If you receive Irinotecan in combination with cetuximab, please consult the cetuximab leaflet. Irinotecan must not be administered earlier than 1 hour after the end of the cetuximab infusion. Please follow the advice of your doctor regarding your current treatment.
If you receive Irinotecan in combination with bevacizumab, please consult the bevacizumab leaflet. These dosages may be adjusted by your doctor depending on your condition and any side-effects you may have.
If you receive Irinotecan in combination with capecitabine, please consult the capecitabine leaflet. These dosages may be adjusted by your doctor depending on your condition and any side-effects you may have.

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 of these side-effects must be treated immediately.

Very common side effects (more than 1out of 10 patients):
IN MONOTHERAPY:
- Neutropenia (reduced white cell count) which increases the risk of infections
- Anaemia (reduction in the number of red blood cells) which can make the skin
  pale and causes weakness and breathlessness
- Decreased appetite
- Cholinergic syndrome: the main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, red, sore, itching or weeping eyes (conjunctivitis), running nose (rhinitis), low blood pressure (hypotension), widening of the blood vessels (vasodilation), sweating, chills, a feeling of general discomfort and illness (malaise), dizziness, visual disturbances, pupil contraction (myosis), watering eyes (lachrymation) and increased salivation occurring during
  or within the first 24 hours after the infusion of Irinotecan. These symptoms disappear after atropine administration
- Diarrhoea
- Vomiting
- Nausea
- Abdominal pain
- Hair loss (hair will grow again after treatment is finished).
- Mucosal inflammation
- Fever
- Asthenia (lack or loss of strength).

IN COMBINATION THERAPY
- Thrombocytopenia (reduction in the number of blood platelets) causing bruises, tendency to bleed and abnormal bleeding
- Neutropenia
- Anaemia
- Decreased appetite
- Cholinergic syndrome: the main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, red, sore, itching or weeping eyes (conjunctivitis), running nose (rhinitis), low blood pressure (hypotension), widening of the blood vessels (vasodilatation), sweating, chills, a feeling of general discomfort and illness (malaise), dizziness, visual disturbances, pupil contraction (myosis), watering eyes (lacrimation) and increased salivation occurring during or within the first 24 hours after the infusion of Irinotecan. These symptoms disappear after atropine administration.
- Diarrhoea
- Vomiting
- Nausea
- Hair loss (hair will grow again after treatment is finished).
- Mucosal inflammation
- Asthenia (lack or loss of strength
- Transient and mild to moderate increase in serum levels of some liver enzymes (SGPT, SGOT, alkaline phosphatase) or bilirubin.

Common side effects (less than 1 out of 10 patients, but more than 1 out of 100):
IN MONOTHERAPY
- Infection
- Thrombocytopenia (reduction in the number of blood platelets) causing bruises, tendency to bleed and abnormal bleeding
- Fever associated with a severe decrease in the number of some white blood cells (febrile neutropenia)
- Constipation
- Transient and mild to moderate increase of serum levels of creatinine
- Transient and mild to moderate increase in serum levels of some liver enzymes (transaminases, alkaline phosphatase) or bilirubin.

IN COMBINATION THERAPY
- Infection
- Fever associated with a severe decrease in the number of some white blood cells (febrile neutropenia)
- Abdominal pain
- Constipation
- Fever.

Rare side effects (less than 1 out of 1,000 patients, but more than 1 out of 10,000):
IN COMBINATION THERAPY:
- Hypokalemia and hyponatremia mostly related with diarrhea and vomiting.

The following information is intended for healthcare professionals only

Irinotecan 20 mg/ml

Concentrate for solution for infusion

irinotecan hydrochloride, trihydrate

Handling:
As with other antineoplastic/cytotoxic agents, Irinotecan must be prepared and handled with caution. The use of goggles, mask and gloves is mandatory.
In case of skin contact with the concentrate or diluted solution, wash immediately and thoroughly with soap and water. If Irinotecan solution or infusion solution should came into contact with the mucous membranes, wash immediately with water.

Instructions for dilution:
As with any other injectable drugs, Irinotecan solution must be prepared aseptically.
If any precipitate is observed in the original vials or after reconstitution, the product should be discarded according to standard procedures for cytotoxic agents.

Aseptically withdraw the required amount of Irinotecan solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 0.9 % sodium chloride solution or 5% glucose solution.
The infusion should then be thoroughly mixed by manual rotation.

Instructions for protection for dilution:
The preparation should be performed in a defined area for manipulation of the drug (preferably under system of vertical laminar air flow). The working area should be protected by coating with disposable absorbent paper and plastic.
Protective
clothing should be used: protective goggles, hair cap, gown and gloves and disposable masks.

Open containers such as bottles of the injection and infusion bottles and tubes, syringes, catheters and tubes used, as well as cytotoxic waste, should be

Frequency not known (cannot be estimated from available data)
- Bowel inflammation causing abdominal pain and/or diarrhoea (a condition known as pseudomembranous colitis)
- Sepsis (life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs)
- Peripheral thrombocytopenia with antiplatelet antibodies
- Loss of water (dehydration), commonly associated with diarrhoea and/or vomiting
- Hypovolaemia (decrease in volume of blood plasma)
- Hypersensitivity (Allergic) reactions
- Severe allergic reactions (anaphylactic/anaphylactoid reactions) including swelling of the hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or breathing. Please contact your doctor immediately if you experience any of these side-effects
- Anaphylactic reactions
- Transient speech disorders, in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan
- Early effects such as muscular contraction or cramps and numbness (paresthesia)
- Increased blood pressure (hypertension) during or following the infusion
- Kidney problems (renal insufficiency), low blood pressure (hypotension) or collapse (cardio-circulatory failure) in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting or sepsis
- Lung disease (interstitial pulmonary disease) presenting as shortness of breath, dry cough, and inspiratory crackles
- Breathing difficulties
- Hiccups (involuntary contraction of the diaphragm that may repeat several times per minute)
- Partial or complete blockage of the bowel (intestinal obstruction, ileus)
- Gastrointestinal bleeding or haemorrhage
- Inflammation of the large bowel causing abdominal pain (colitis including typhlitis, ischemic and ulcerative colitis)
- Abnormal dilation of the colon (Megacolon)
- Symptomatic or asymptomatic elevated pancreatic enzymes
- Intestinal perforation
- Skin reactions
- Infusion site reactions
- Increase in levels of some digestive enzymes which break down sugars (amylase) or fats (lipase)
- Hypokalaemia
- Hyponatremia mostly related with diarrhoea and vomiting
- Increase in serum levels of some liver enzymes (transaminases, i.e. AST and ALT) in the absence of progressive liver metastasis have been very rarely reported
- Muscular contraction or cramps.
- Fungal infections
- Viral infections

If you receive Irinotecan in combination with cetuximab, some of the side effects you may experience can also be related to these combinations. 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 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 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.

It is necessary to tell your doctor if you experience:
- "early" diarrhoea with associated symptoms referred to as "the acute cholinergic syndrome" (see Section 2)
- "delayed" diarrhoea
- diarrhoea persisting for 48 hours after treatment initiation
- fever
- nausea, vomiting
- respiratory disorders, non-productive cough, symptoms of crepitations in the lungs.

Patient's hospitalisation is indicated in the following situations:
- diarrhoea and coexisting fever (over 38°C)
- severe diarrhoea (and vomiting) with clinical features of excessive dehydration (intravenous fluid replacement is necessary)
- diarrhoea not subsiding within 48 hours of treatment initiation.

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 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 IRINOTECAN

Keep this medicine out of the sight and reach of children.
Store below 25°C. Store in the original package in order to protect from light.
For single use only.
After dilution with 5% glucose, physical and chemical stability was demonstrated for 24 hours, when stored between 2–8ºC and for 12 hours when stored at 25 ±2ºC, protected from light.
After dilution with 0.9% sodium chloride, physical and chemical stability was demonstrated for 24 hours, when stored between 2-8ºC and for 12 hours when stored at 25±2ºC, protected from light.
Irinotecan should be diluted and used immediately after opening.
From a microbiologic point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility
of user.
Do not use this medicine after the expiry date which is stated on the label and
carton after EXP. The expiry date refers to the last day of that month.
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 to protect the environment

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Irinotecan contains
The active substance of Irinotecan is irinotecan hydrochloride, trihydrate.
1 ml of concentrate contains 20mg of irinotecan hydrochloride, trihydrate
(equivalent to 17.33mg/ml of irinotecan).
One vial of 2ml contains 40mg of irinotecan hydrochloride, trihydrate.
One vial of 5ml contains 100mg of irinotecan hydrochloride, trihydrate.
One vial of 15ml contains 300mg of irinotecan hydrochloride, trihydrate.
One vial of 25ml contains 500mg of irinotecan hydrochloride, trihydrate.

The other ingredients are sorbitol (E420), lactic acid, sodium hydroxide and/or hydrochloric acid (for pH adjustment to 3.5) and water for injection.

Irinotecan is a yellow clear solution.
pH: 3.0 – 4.0
Osmolality: 265-350 mosmol/kg

What Irinotecan looks like and contents of the pack
Amber glass vial, with FluroTec rubber stopper or equivalent and aluminium
flip-off cap.

Package size:
Pack with 1 vial of 2 ml – Pack with 1 vial of 5 ml – Pack with 1 vial of 15 ml – Pack with 1 vial of 25 ml
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó, nº 8, 8A – 8B Fervença 2705 – 906 Terrugem SNT, Portugal

Manufacturer
Thymoorgan Pharmazie GmbH
Schiffgraben 23, D-38690 Goslar, Germany

Distributor:
Consilient Health (UK) Ltd.
No. 1 Church Road, Richmond upon Thames, Surrey.
TW9 2QE

This medicine product is authorised in the Member States of the EEA under the following names:

Austria:	Irinotecan Hikma 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium:	Irinotecan Hikma 20 mg/ml
France:	Irinotecan Hikma 20 mg/ml, solution à diluer pour perfusion
Germany:	Riboirino 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Italy:	rinto 20mg/ml Concentrato per Soluzione per InfusioneIrinto
Netherlands:	Irinotecan HCl trihydraat Hikma 20 mg/ml concentraat voor oplossing voor infusie
Portugal:	Irinotecano Hikma
Spain:	Irinotecán Hikma 20 mg/ml Concentrado para Solución para perfusión EFG
United Kingdom:	Irinotecan 20mg/ml Concentrate for solution for infusion

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considered hazardous waste and be disposed of in accordance with local guidelines for handling of HAZARDOUS waste.

In case of spillage, protective clothing should be used. Broken glass should be collected and placed in hazardous waste containers. The contaminated surfaces should be properly rinsed with abundant amounts of cold water and thoroughly cleaned. The materials used for cleaning should be disposed of as hazardous waste.

In case Irinotecan comes into contact with the skin, the area should be rinsed profusely with running water and then washed with soap and water. In case of contact with mucous membranes, wash thoroughly the affected area contacted
with water. If you feel some unease, contact a doctor.
In case of eye contact with Irinotecan, wash them thoroughly with plenty of water. Contact an ophthalmologist immediately.

Disposal:
All materials used for dilution and administration should be disposed of according
to hospital standard procedures applicable to cytotoxic agents.