Package leaflet: Information for the user

Irinotecan Hydrochloride 20 mg/ml
Concentrate for 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. 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 belongs to a group of medicines called cytostatics (anti-cancer medicines).

This medicine is used for the treatment of advanced cancer of colon and rectum in adults and where the disease is at an advanced stage in the large intestine, either in combination with other medicines (combination therapy) or alone (monotherapy).

Your doctor may use a combination of irinotecan with 5-fluorouracil/ folinic acid (5FU/FA) and bevacizumab to treat your cancer of the colon and rectum.

Your doctor may use a combination of irinotecan with capecitabine with or without bevacizumab to treat your cancer of the colon and rectum.

Your doctor may use a combination of irinotecan with cetuximab to treat cancer of the large intestine (KRAS wild-type) that is of a certain type known to display cell markers referred to as epidermal growth factor receptors (EGFR) which are blocked by the cetuximab.

If you need any further information on your condition, please ask your doctor.

2. What you need to know before you use Irinotecan

Do not use Irinotecan:
- if you are allergic to irinotecan hydrochloride trihydrate or any of the other ingredients of this medicine (listed in section 6)
- if you have any other bowel disease or a history of bowel obstruction
- if you are breast feeding
- if you have increased levels of bilirubin in the blood (more than 3 times the upper limit of normal range)
- if you have an imbalance of your blood cells (severe bone marrow failure)
- if you are in a poor general health (evaluated by a international standard)
- if you are using natural remedy St John's Wort (*hypericum perforatum*)

Warnings and precautions:

Special care is also needed in elderly patients due to their greater frequency of decreased biological functions.

As irinotecan is an anti-cancer medicine it will be administered to you in a special unit and under the supervision of a doctor qualified in the use of anti cancer medicines. The unit's personnel will explain to you what you need to take special care of during and after the treatment. This leaflet helps you to remember that.

If you receive irinotecan in combination with cetuximab or bevacizumab or capecitabine, please make sure that you also read the package leaflet for these medicinal products.
Before you use this medicine tell your doctor if any of the following apply to you:
- if you have liver problems or jaundice
- if you have kidney problems
- if you have asthma
- if you have ever received radiation therapy
- if you experienced severe diarrhoea or fever after being treated with irinotecan before.
- if you have heart problems
- if you smoke, have high blood pressure or high cholesterol as these can increase the risk of heart problems during treatment with this medicine
- if you have had or are due to have any vaccinations
- if you are taking any other medicines. Please see the section below "Other medicines and Irinotecan".

During administration of Irinotecan (30 – 90 minutes) and up to 24 hours after administration you may experience some of the following symptoms:
- Diarrhoea
- Sweating
- Abdominal pain
- Feeling unwell (nausea)
- Watering eyes
- Visual disturbance
- Excessive mouth watering
- low blood pressure

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

Diarrhoea
If your diarrhoea starts more than 24 hours after administration of Irinotecan ("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:
1. Take any antidiarrhoeal 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 antidiarrhoeal 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.
2. Drink large amounts of water and rehydration fluids immediately (i.e. water, soda water, fizzy drink, soup or oral rehydration therapy).
3. 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 doctor's instruction. The anti-diarrhoeal treatment should not be used preventive, even though you have experienced delayed diarrhoea at previous cycles.

Fever
If the body temperature increases over 38°C it may be a sign of infection, especially if you also have diarrhoea. If you have any fever (over 38°C) contact your doctor or the unit immediately so that they can give you any treatment necessary.

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

Neutropenia
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.

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).

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 problem.

If you have one or more of the symptoms mentioned, after you have returned home from the hospital, you should immediately contact the doctor or the unit supervising the irinotecan treatment.

Other medicines and Irinotecan
Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is also valid for herbal medicines.

The following medications can alter the effects of irinotecan:
- carbamazepine, phenobarbital or phenytoin (medicines used in the management of epilepsy)
- ketoconazole (used for the treatment of fungal infections)
- rifampicin (used for the treatment of tuberculosis)
- the herbal medicine St John's wort (*hypericum perforatum*) must not be used during treatment with irinotecan and not between treatments, as it may decrease the effect of irinotecan.
- atazanavir (used to treat HIV)
- warfarin (an anticoagulant used to thin the blood)
- vaccines. Tell your doctor if you have had or are due to have any vaccinations
- ciclosporin or tacrolimus (used for prevention of graft rejection)

If you require an operation, please tell your doctor or anaesthetist that you are using this medicine, as it may alter the effect of some medicines used during surgery.

Pregnancy and breast-feeding

Pregnancy

You must not use irinotecan if you are pregnant unless your doctor considers it clearly necessary, as it may harm your unborn baby. You should also avoid becoming pregnant while you are being treated with irinotecan.

If you do become pregnant while being treated with irinotecan you must inform your doctor IMMEDIATELY.

Contraception in males and females
Men and women should use adequate contraception while being treated with irinotecan and for:
- up to 1 month after you receive your last dose of irinotecan if you are female
- up to 3 months after your last dose of irinotecan if you are male.

Breast-feeding
Because irinotecan may be harmful to nursing infants, women must not breastfeed while being treated with irinotecan.

Driving and using machines
In some cases Irinotecan may cause side effects which affect the ability to drive and use tools and machines.

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 use any tools or operate machinery.

Irinotecan contains sorbitol and sodium
If you have been told by your doctor that you have an intolerance to some sugars (e.g. fructose intolerance), contact your doctor before you take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per does, i.e. is essentially 'sodium free'.

3. How to use Irinotecan

For adults only.

Irinotecan will be given as an infusion into your veins over a period of 30 to 90 minutes.

The amount of infusion you are given will depend on your age, height, weight and general medical condition. It will also depend on any other treatment you may have received for your cancer. Your doctor will calculate your body surface area in square meters (m^2) from your height and weight.
- 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 3 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.

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 cetuximab, 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 more Irinotecan than you should
In case you were given a higher dosage of irinotecan than required the occurring side effects may be more severe. You will get maximum supportive care to prevent dehydration due to diarrhoea and to treat any infectious complication. If you think you have been administered an overdose please contact your doctor.

If you miss a dose of Irinotecan
It is very important to receive all scheduled doses. If you miss a dose, contact your doctor promptly.

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 of these side effects must be treated immediately. These are:

Very common: may affect more than 1 in 10 people
- in monotherapy, fever
- blood disorders including abnormally low number of neutrophil granulocytes, a type of white blood cell (neutropenia) causing fever, sore mouth, gum pain & swelling, cough, etc.
- severe diarrhea
- severe nausea (feeling sick) and vomiting (being sick)
- severe transient acute cholinergic syndrome: the main symptoms are 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; flushing due to widening of the blood vessels (vasodilation); sweating, chills; a feeling of

The following information is intended for healthcare professionals only:

Instructions for use -
Cytotoxic

Handling of Irinotecan
As with other neoplastic agents, caution should be exercised when handling Irinotecan. Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Precautions should be taken to avoid contact with the skin and mucous membranes.
Protection instructions for preparation of Irinotecan solution for infusion
1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available mouth cover and goggles should be used.
2. Opened containers, like injection vials and infusion bottles and used cannulae, syringes, catheters, tubes, and residuals of cytostatics should be considered as hazardous waste and undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.
3. Follow the instructions below in case of spillage:
   - protective clothing should be worn
   - broken glass should be collected and placed in the container for HAZARDOUS WASTE.
   - contaminated surfaces should be flushed properly with copious amount of cold water
   - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE
4. In the event of Irinotecan contact with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact doctor.
5. In case of contact of Irinotecan with eyes wash them thoroughly with plenty of water. Contact an ophthalmologist immediately.

Preparation for the infusion solution
Irinotecan concentrate for solution for infusion is intended for intravenous infusion only after diluting prior to administration in the recommended diluents, either 0,9 % Sodium chloride solution for infusion or 5% glucose solution for infusion. Aseptically withdraw the required amount of Irinotecan concentrate for solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle. The infusion should be thoroughly mixed by manual rotation.
If any precipitate is observed in the vials or after reconstitution, the product should be discarded according to standard procedure for cytotoxic agents.
Irinotecan should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

Disposal
All items used for preparation, administration or otherwise coming into contact with Irinotecan should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

general discomfort and illness, dizziness; visual disturbances, pupil contraction; watering eyes and increased salivation, occurring during or within the first 24 hours after the infusion of irinotecan.

Common: may affect up to 1 in 10 people
- in combination therapy, fever infections associated with a severe decrease in the number of some white blood cells (neutropenia)
- fever associated with a severe decrease in the number of some white blood cells (febrile neutropenia)

Not known: frequency cannot be estimated from the available data
- allergic reaction (skin rash including red itchy skin, urticaria, conjunctivitis, rhinitis)
- severe allergic reactions (anaphylatic/ anaphylactoid reaction), including swelling of the hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or extreme difficulty breathing
- symptomatic and asymptomatic inflammation of the pancreas (mainly abdominal pain)
- lung disease presenting as shortness of breath, dry cough, and inspiratory crackles (interstitial pulmonary disease)

Please read instructions, described in section "Warnings and precautions" carefully and follow them if you have any of the side-effects listed above.

Other side effect includes:

Very common: may affect more than 1 in 10 people
- in combination therapy, thrombocytopenia (reduction in the number of blood platelets) causing bruises, tendency to bleed and abnormal bleeding
- reduction of the quantity of haemoglobin in blood (anaemia) causing fatique, shortness of breath, headache, pale skin, dizziness, leg cramps, etc.
- hair loss (the hair grows again after end of treatment)
- in combination therapy, transient and mild to moderate increase in serum levels of some liver enzymes (SGPT, SGOT, alkaline phosphatase) or bilirubin
- abnormal physical weaknes (Asthenia)
- swelling or irritation of the mucus membranes (Mucosal inflammation)
- in monotherapy, abdominal (stomach) pain
- decreased appetite

Common: may affect up to 1 in 10 people
- constipation
- in monotherapy, thrombocytopenia (reduction in the number of blood platelets) causing bruises, tendency to bleed and abnormal bleeding
- in monotherapy, increased level of liver enzymes, bilirubin and creatinine in the blood.
- In combination therapy, abdominal (stomach) pain

Not known: frequency cannot be estimated from the available data
- thrombosis/embolism
- muscular contractions or cramps
- paraesthesia (abnormal sensation such as tingling or numbness)
- loss of water (dehydration), commonly associated with diarrhoea and /or vomiting
- mild skin reactions and mild reactions at the infusion site
- partial or complete blockage of the bowel (intestinal obstruction, ileus), stomach and intestines bleeding
- bowel inflammation causing abdominal pain and/or diarrhoea (a condition known as pseudo-membraneous colitis)
- renal insufficiency (renal failure), low blood pressure or cardio-circulatory failure in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting or sepsis (blood infection)
- inflammation of the large bowel causing abdominal pain (colitis including typhlitis, ischemic and ulcerative colitis)
- intestinal perforation (a hole through the wall of the intestine)
- decreased levels of potassium and sodium in the blood, mostly related to diarrhoea and vomiting
- increase in levels of some digestive enzymes, which break down sugars (amylase) and fats (lipase)
- increased blood pressure during and following administration
- transient speech disorders
- hypovolaemia (decreased blood volume)
- hiccups (involuntary contractions of the diaphragm muscle)
- Dyspnoea (shortness of breath)

If you receive Irinotecan in combination with cetuximab, some of the side effects you may experience can also be related to this combination. Such side effects may include a 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 you may experience can also be related to this combination. Such side effects may include: blood clots (very common), allergic reactions, heart attack and fever in patients with a low white blood cell count (common). 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 (common). 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

For the UK
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

For Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
www.hpra.ie
medsafety@hpra.ie

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.

For single use only.
Store below 25°C. Store in the original package in order to protect from light. Do not freeze.

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

The product should be diluted and used immediately after opening. If prepared aseptically, the diluted solution can be stored for 24 hours at temperature up to 15-25ºC and for 48 hours at 2-8ºC .

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions 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 has taken place in controlled and validated aseptic conditions.

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 Hydrochloride 20 mg/ml Concentrate for Solution for Infusion contains: The active substance is irinotecan hydrochloride trihydrate. 1 ml of concentrate contains 20 mg irinotecan hydrochloride trihydrate equivalent to 17.33 mg of irinotecan.
One 2 ml vial contains 40 mg irinotecan hydrochloride trihydrate
One 5 ml vial contains 100 mg irinotecan hydrochloride trihydrate
One 15 ml vial contains 300 mg irinotecan hydrochloride trihydrate
One 25 ml vial contains 500 mg irinotecan hydrochloride trihydrate
The other ingredients are sorbitol E420, lactic acid, sodium hydroxide, hydrochloric acid and water for injections.

What Irinotecan Hydrochloride 20 mg/ml Concentrate for Solution for Infusion looks like and contents of the pack:
Irinotecan 20 mg/ml Concentrate for Solution for Infusion is a clear, pale yellow coloured solution.

Pack size:
1× 2 ml vial, 1 × 5 ml vial , 1 x 15 ml vial , 1 × 25 ml vial
Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

For UK:
Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road, Bordon
Hampshire, GU35 0NF
United Kingdom

For IRL :
Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

Manufacturers:
Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, HA1 4HF, UK

Or

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road, Bordon
Hampshire, GU35 0NF
United Kingdom

Fresenius Kabi Deutschland GmbH
Pfingstweide 53
61169 Friedberg
Germany

This medicinal product is authorized in the member states of the EEA under the following names:

Austria	Irinotecan Fresenius 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Irinokabi 20 mg/ml concentraat voor oplossing voor infusie
Czech Republic	Irinotecan Fresenius 20 mg/ml koncentrát pro infuzní roztok
Germany	Irinotecan Fresenius 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Denmark	Irinokabi
Estonia	Irinotecan Fresenius
Spain	Irinotecan Fresenius 20 mg/ml concentrado para solución para perfusión EFG
Hungary	Irinotecan Fresenius 20 mg/ml koncentrátum oldatos infúzióhoz
Ireland	Irinotecan Hydrochloride 20 mg/ml Concentrate for Solution for Infusion
Italy	Irinotecan Fresenius
Latvia	Irinotecan Fresenius 20 mg/ml koncentrāts infūziju šķīduma pagatavošanai
Lithuania	Irinotecan Fresenius 20 mg/ml koncentratas infuziniam tirpalui
The Netherlands	Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml concentraat voor oplossing voor infusie
Norway	Irinokabi
Poland	Irinotecan Fresenius
Portugal	Irinotecano Fresenius
Sweden	Irinokabi
Slovak Republic	Irinotecan Fresenius 20 mg/ml infúzny koncentrát
United Kingdom	Irinotecan Hydrochloride 20 mg/ml Concentrate for Solution for Infusion

The leaflet was last revised in February 2018