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, or pharmacist or nurse
- 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Irinotecan Hydrochloride is and what it is used for

Irinotecan Hydrochloride belongs to a group of medicines called cytostatics (anti-cancer medicines).
Irinotecan Hydrochloride 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 (5-FU/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 monoclonal antibody.

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

2. What you need to know before you use Irinotecan Hydrochloride

Do not use Irinotecan Hydrochloride:
- if you are hypersensitive (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 the 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 an international standard)
- if you are using the natural remedy St John´s wort (*Hypericum perforatum*)

For additional contraindications of cetuximab or bevacizumab or capecitabine, which may be used in combination with irinotecan, please refer to the product information for these medicinal products.

Warnings and precautions:

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.

As Irinotecan Hydrochloride is an anti-cancer medicine it will be administered to you in a special unit and under supervision of a doctor qualified in the use of anti-cancer medicines. The units' 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.

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 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

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
- watering eyes
- 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.
These 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 must 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 must not be taken for more than 48 hours.
2. Drink large amounts of water and rehydration fluids, immediately (i.e. water, soda water, fizzy drinks, 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 hospital unit 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 instructions. The antidiarrhoeal treatment should not be used as a preventive, even if 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 hospital 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 problems.

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

Other medicines and Irinotecan Hydrochloride

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 (drugs 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)
- Anticoagulants (used to thin the blood)
- Vaccines. Tell your doctor if you have had or are due to have any vaccinations
- Ciclosporin or tacromilus (used to dampen down your body's immune system)

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:

Do not use Irinotecan Hydrochloride:

- If you are breast-feeding

You should not be given irinotecan if you are pregnant, unless your clinical condition requires treatment with irinotecan.
If you or your partner is being treated with irinotecan you must avoid becoming pregnant during treatment. Women of childbearing potential and men should use adequate contraception while being treated and for at least:

- one month after cessation of therapy for women

or

- three months after cessation of treatment for men

Still, if you become pregnant, during this period you must immediately inform your doctor.

Driving and using machines

In some cases Irinotecan Hydrochloride may cause side effects which affect your 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 Hydrochloride you may feel dizzy or have visual disturbances. If this happens to you do not drive or operate machinery.

Irinotecan Hydrochloride contains sorbitol. 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 also contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

3. How to take Irinotecan Hydrochloride

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

For adults only.

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

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

- 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.

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

Please follow the advice of your doctor regarding your current treatment.

These dosages may be adjusted by your doctor depending on your condition and any side-effects you may have.

If you use more Irinotecan Hydrochloride than you should receive:

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 have any further questions on the use of this medicine, ask your doctor or 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:

- diarrhoea
- a decrease in the number of neutrophil granulocytes, a type of white blood cell, which plays an important role in fighting infections.
- fever
- nausea and vomiting
- breathing difficulties (possible symptom of severe allergic reactions)

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 effects include:

Very common side effects (more than 1 in 10 patients)

- blood disorders including abnormally low number of neutrophil granulocytes, a type of white blood cell (neutropenia) and reduction of the quantity of haemoglobin in blood (anaemia)
- in combination therapy, thrombocytopenia (reduction in the number of blood platelets) causing bruises, tendency to bleed and abnormal bleeding
- in monotherapy, fever
- in monotherapy, infections
- delayed severe diarrhoea
- in monotherapy, severe nausea (feeling sick) and vomiting (being sick)
- 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

Common side effects (less than 1 in 10 patients but more than 1 in 100)

- 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 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 Hydrochloride
- in monotherapy, thrombocytopenia (reduction in the number of blood platelets) causing bruises, tendency to bleed and abnormal bleeding
- in combination therapy, fever
- in combination therapy, infections
- infections associated with a severe decrease in the number of some white blood cells (neutropenia) resulting in death in 3 cases
- fever associated with a severe decrease in the number of some white blood cells (febrile neutropenia)
- in combination therapy, severe nausea (feeling sick) and vomiting (being sick)
- loss of water (dehydration), commonly associated with diarrhoea and /or vomiting
- constipation
- feeling week (asthenia)
- in monotherapy, transient and mild to moderate increase in serum levels of some liver enzymes (transaminases, alkaline phosphatase) or bilirubin
- transient and mild to moderate increase of levels of creatinine in the blood
- in combination therapy, transient pronounced (grade 3) increase in serum levels of bilirubin

Uncommon side effects (less than 1 in 100 patients but more than 1 in 1,000)

- mild allergic reaction (skin rash including red itchy skin, urticaria, conjunctivitis, rhinitis)
- mild skin reactions
- mild reactions at the infusion site
- lung disease presenting as shortness of breath, dry cough, and inspiratory crackles (interstitial pulmonary disease); early effects such as breathing difficulties
- 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, low blood pressure or cardio-circulatory failure in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting or sepsis

Rare side effects (less than 1 in 1,000 patients but more than 1 in 10,000)

- 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
- muscular contraction or cramps and numbness (paraesthesia)
- inflammation of the large bowel causing abdominal pain (colitis including typhlitis, ischemic and ulcerative colitis)
- intestinal perforation
- loss of appetite
- abdominal pain
- inflammation of the mucous membranes
- decreased levels of potassium and sodium in the blood, mostly related to diarrhoea and vomiting
- symptomatic and asymptomatic inflammation of the pancreas (mainly abdominal pain)
- increased blood pressure during and following administration

Very rare effects (less than 1 in 10,000 patients)
- transient speech disorders
- increase in levels of some digestive enzymes which break down sugars (amylase) and fats (lipase)
- one case of low platelet count in the blood due to antibodies against platelets

Side effects of unknown frequency:
- rash
- abnormally low number of white blood cells (leukopenia).
- 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 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 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 and bevacizumab. .

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.

Reporting of Side Effects
If you get any of the 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Irinotecan Hydrochloride

- 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 label and carton. The expiry date refers to the last day of that month.
- Concentrate: Keep vials in the outer carton in order to protect from light. Do not freeze. Once opened vials should be used immediately as they contain no antimicrobial preservatives.
- Diluted concentrate: For single use only. Unused solution should be discarded
- Following dilution: Chemical and physical in-use stability has been demonstrated in glucose 50 mg/ml (5%) and sodium chloride 9 mg/ml (0.9%) for 72 hours at 2-8 °C. 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 dilution has taken place in controlled and validated aseptic conditions.

Do not use this medicine if you notice particles visible in the concentrate or infusion solution.

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 Hydrochloride contains

- The active substance is irinotecan hydrochloride trihydrate. Each millilitre (ml) of solution contains 20 milligrams (mg) of irinotecan hydrochloride trihydrate, equivalent to 17.33 mg irinotecan.
- The other ingredients are sorbitol (E420), lactic acid, Water for Injections, and sodium hydroxide and hydrochloric acid (used to adjust pH).

What Irinotecan Hydrochloride looks like and contents of the pack

Irinotecan Hydrochloride is in the form of a concentrate for solution for infusion (a concentrated solution which is diluted to make a solution which is given as a slow infusion via a drip).

The medicine comes in glass containers called vials, containing 2 ml, 5 ml and 25 ml of irinotecan hydrochloride trihydrate.
The vials are wrapped in a protective plastic to reduce the risk of spillage if the vials break - these are referred to as ONCO-TAIN® vials.

The vials are available in single packs. Not all presentations may be marketed.

Marketing Authorisation Holder and Manufacturer:
Hospira UK Limited
Horizon
Honey Lane
Hurley
Maidenhead
SL6 6RJ
United Kingdom

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The following information is intended for healthcare professionals only

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

As with other potentially toxic compounds, caution should be exercised when handling and preparing irinotecan solutions.

Instructions for use/handling
As with other antineoplastic agents, irinotecan must be prepared and handled with caution. The use of goggles, mask and gloves is required. Pregnant women should not handle cytotoxics. If irinotecan concentrate or infusion solutions should come into contact with the skin, it must be washed off immediately and thoroughly with soap and water. If irinotecan concentrate or infusion solutions should come into contact with the mucous membranes, it must be washed off immediately with water.

Preparation of the intravenous infusion
As with any other infusions**,** irinotecan infusion must be prepared using aseptic technique**.**

If any precipitate is observed in the vials or in the infusion solution, the product must be discarded according to standard procedures for discarding cytotoxic agents.

Aseptically withdraw the required amount of irinotecan concentrate from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 9 mg/ml (0.9%) sodium chloride solution or 50 mg/ml (5%) glucose solution only. The infusion should then be thoroughly mixed by manual rotation.

Disposal
All materials used for dilution and administration should be disposed of according to local procedures applicable to the discarding of cytotoxic agents.