LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Summary Public Assessment Report

Irinotecan Actavis
(irinotecan)

SE/H/1728/001/E/001

The Summary Public Assessment Report was written in 2007 by the previous RMS UK after initial procedure UK/H/1013/001/DC and is attached at the end of this document. RMS transfer from UK to SE was completed 2017-09-01.

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Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Irinotecan Actavis 20mg/ml Concentrate for Solution for Infusion

UK/H/1013/001/DC
UK licence no: PL 21231/0024

Actavis Group hf

LAY SUMMARY

The MHRA today granted Actavis Group hf a Marketing Authorisation (licence) for the medicinal product Irinotecan Actavis. This is a prescription-only medicine (POM) that is used for the treatment of advanced cancer of the colon and rectum in adults, either alone or in a combination with other medicines.

Irinotecan Actavis contains the active ingredient irinotecan hydrochloride trihydrate, which belongs to a group of medicines called cytostatics (anti-cancer medicines).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Irinotecan Actavis outweighs the risks, hence a Marketing Authorisation has been granted.

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II. MODULE 1

Product Name	Irinotecan Actavis 20mg/ml concentrate for solution for infusion
Type of Application	Generic, Article 10.1
Active Substance	Irinotecan Hydrochloride Trihydrate
Form	Concentrate for solution for infusion
Strength	20mg/ml
MA Holder	Actavis Group hf, Reykjavikurvegi 76-78, Hafnarfjordur, IS-220, Iceland
RMS	UK
CMS	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Norway, Poland, Portugal, Slovenia, Slovak Republic, Spain and Sweden
Procedure Number	UK/H/1013/001/DC
Timetable	Day 210 – 19th September 2007

III. MODULE 2 SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Irinotecan Actavis 20 mg/ml concentrate for solution for infusion

III.1 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 20mg Irinotecan hydrochloride trihydrate equivalent to 17.33 mg/ml irinotecan. Each 2ml or 5ml vial of Irinotecan Actavis contains 40mg or 100mg of Irinotecan hydrochloride trihydrate respectively.
Excipients:
Sorbitol E420
Sodium
For a full list of excipients, see section 6.1.

III.2 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion:

A clear, colourless to slightly yellow solution.

III.3 4 CLINICAL PARTICULARS

III.3.1 4.1 Therapeutic indications

Irinotecan Actavis is indicated for the treatment of patients with advanced colorectal cancer:

- in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease,
- as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

Irinotecan in combination with cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

Irinotecan in combination with 5-fluorouracil, folinic acid and bevacizumab is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

III.3.2 4.2 Posology and method of administration

For adults only. After dilution Irinotecan Actavis solution for infusion should be infused into a peripheral or central vein. ***Recommended dosage***

III.3.3 In monotherapy (for previously treated patient)

The recommended dosage of irinotecan hydrochloride trihydrate is 350 mg/m² administered as an intravenous infusion over a 30- 90 minute period every three weeks (see below "Method of administration" and section 4.4 and 6.6).

III.3.4 In combination therapy (for previously untreated patient)

Safety and efficacy of irinotecan in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with the following schedule (see section 5.1): Irinotecan plus 5FU/FA in every 2 weeks schedule.

The recommended dose of irinotecan hydrochloride trihydrate is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30-90 minute period, followed by infusion with folinic acid and 5-fluorouracil.

For the posology and method of administration of concomitant cetuximab, refer to the product information for this medicinal product.

Normally, the same dose of irinotecan is used as administered in the last cycles of the prior irinotecan-containing regimen. Irinotecan must not be administered earlier than 1 hour after the end of the cetuximab infusion.

For the posology and method of administration of bevacizumab, refer to the bevacizumab summary product of characteristics.

III.3.5 Dosage adjustments

Irinotecan should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-related diarrhoea is fully resolved.

At the start of a subsequent infusion of therapy, the dose of Irinotecan Actavis, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15 to 20 % should be applied for irinotecan hydrochloride trihydrate and/or 5FU when applicable:
- haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3-4 and fever grade 2-4), thrombocytopenia and leukopenia (grade 4)), - non haematological toxicity (grade 3-4).

Recommendations for dose modifications of cetuximab when administered in combination with irinotecan must be followed according to the product information for this medicinal product.

Refer to the bevacizumab summary product of characteristics for dose modifications of bevacizumab when administered in combination with Irinotecan/5FU/FA.

Treatment Duration:
Treatment with irinotecan should be continued until there is an objective progression of the disease or an unacceptable toxicity.

III.3.6 Special populations

III.3.6.1 Patients with impaired hepatic function

In monotherapy: Blood bilirubin levels (up to 3 times the upper limit of the normal range (ULN)) in patients with performance status ≤ 2, should determine the starting dose of Irinotecan Actavis. In these patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased (see section 5.2) and therefore the risk of hematotoxicity is increased. Thus, weekly monitoring of complete blood counts should be conducted in this patient population.

- In patients with bilirubin up to 1.5 times the ULN, the recommended dosage of irinotecan hydrochloride trihydrate is 350 mg/m²,
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of irinotecan hydrochloride trihydrate is 200 mg/m², - Patients with bilirubin beyond 3 times the ULN should not be treated with irinotecan (see section 4.3 and section 4.4).

No data are available in patients with hepatic impairment treated with irinotecan in combination.

III.3.6.2 Patients with impaired renal function

Irinotecan is not recommended for use in patients with impaired renal function, as studies in this population have not been conducted. (See section 4.4 and section 5.2).

III.3.6.3 Elderly

No specific pharmacokinetic studies have been performed in elderly. However, the dose should be chosen carefully in this population due to their greater frequency of decreased biological functions. This population should require more intense surveillance (see section 4.4).

Children
Irinotecan should not be used in children.

III.3.7 Method of administration

Irinotecan Actavis is cytotoxic, for information regarding dilution, and special precautions for disposal and other handling see section 6.6.

Irinotecan Actavis should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

III.3.8 Treatment Duration

Treatment with irinotecan should be continued until there is an objective progression of the disease or an unacceptable toxicity.

III.3.8.1 4.3 Contraindications

- Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).
- History of severe hypersensitivity to irinotecan hydrochloride trihydrate or to any of the excipients.
- Pregnancy and lactation (see section 4.4 and section 4.6).
- Bilirubin >3 times the ULN (see section 4.4).
- Severe bone marrow failure.
- WHO performance status> 2.
- Concomitant use with St John's Wort (see section 4.5).
- For additional contraindications of cetuximab or bevacizumab, refer to the product information for these medicinal products.

III.3.8.2 4.4 Special warnings and precautions for use

The use of Irinotecan Actavis should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

Given the nature and incidence of adverse events, Irinotecan Actavis will only be prescribed in the following cases after the expected benefits have been weighted against the possible therapeutic risks:

- in patients presenting a risk factor, particularly those with a WHO performance status = 2.
- in the few rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea). Strict hospital supervision is recommended for such patients.

When Irinotecan Actavis is used in monotherapy, it is usually prescribed with the every-3-week-dosage schedule. However, the weekly-dosage schedule (see section 5.1) may be considered in patients who may need a closer follow-up or who are at particular risk of severe neutropenia.

III.3.8.3 Delayed diarrhoea

Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan hydrochloride trihydrate. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women. If not properly treated, diarrhoea can be lifethreatening, especially if the patient is concomitantly neutropenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where irinotecan hydrochloride trihydrate has been administered. After discharge from the hospital, the patients should obtain the prescribed drugs so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their physician or the department administering irinotecan hydrochloride trihydrate when/if diarrhoea is occurring.

The currently recommended antidiarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours). This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the anti-diarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm³).

In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea, in the following cases:

- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles (see section 4.2).

III.3.8.4 Haematology

Weekly monitoring of complete blood cell counts is recommended during treatment with irinotecan. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature >38°C and neutrophil count ≤1,000 cells/mm³) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics.

In patients who experienced severe haematological events, a dose reduction is recommended for subsequent administration (see section 4.2).

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. In patients with severe diarrhoea, complete blood cell counts should be performed.

III.3.8.5 Liver impairment

Liver function tests should be performed at baseline and before each cycle.

Weekly monitoring of complete blood counts should be conducted in patients with bilirubin ranging from 1.5 to 3 times ULN, due to decrease of the clearance of irinotecan (see section 5.2) and thus increasing the risk of hematotoxicity in this population. Irinotecan should not be administered to patients with a bilirubin> 3 times ULN (see section 4.3).

III.3.8.6 Nausea and vomiting

A prophylactic treatment with antiemetics is recommended before each treatment with irinotecan. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment.

III.3.8.7 Acute cholinergic syndrome

If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (250 micrograms subcutaneously) should be administered unless clinically contraindicated (see section 4.8). Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan.

III.3.8.8 Respiratory disorders

Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Interstitial pulmonary disease can be fatal. Risk factors possibly associated with the development of interstitial pulmonary disease include the use of pneumotoxic drugs, radiation therapy and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy.

III.3.8.9 Elderly

Due to the greater frequency of decreased biological functions, in particular hepatic function, in elderly patients, dose selection with Irinotecan Actavis should be cautious in this population (see section 4.2).

III.3.8.10 Patients with bowel obstruction

Patients must not be treated with Irintoecan Actavis until resolution of the bowel obstruction (see section 4.3).

Patients with Impaired Renal Function

Studies in this population have not been conducted. (see section 4.2 and section 5.2).

III.3.8.11 Others

Since Irinotecan Actavis contains sorbitol, it is unsuitable in hereditary fructose intolerance.

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.

Contraceptive measures must be taken during and for at least three months after cessation of therapy.

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's Wort) of CYP3A4 may alter the metabolism of irinotecan and should be avoided (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since irinotecan has anticholinesterase activity, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising drugs may be antagonised.

Several studies have shown that concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs was reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of cytochrome P450 3A enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.

A study has shown that the co-administration of ketoconazole resulted in a decrease in the AUC of APC of 87% and in an increase in the AUC of SN-38 of 109% in comparison to irinotecan given alone.

Caution should be exercised in patients concurrently taking drugs known to inhibit (e.g., ketoconazole) or induce (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin) drug metabolism by cytochrome P450 3A4. Concurrent administration of irinotecan with an inhibitor/inducer of this metabolic pathway may alter the metabolism of irinotecan and should be avoided (see section 4.4).

In a small pharmacokinetic study (n=5), in which irinotecan 350 mg/m^2 was coadministered with St. John's Wort (*Hypericum perforatum*) 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentrations was observed. St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with irinotecan (see section 4.3).

Coadministration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

There is no evidence that the safety profile of irinotecan is influenced by cetuximab or *vice versa*.

In one study, irinotecan concentrations were similar in patients receiving irinotecan /5FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of irinotecan, were analyzed in a subset of patients (approximately 30 per treatment arm). Concentrations of SN-38 were on average 33% higher in patients receiving irinotecan /5FU/FA in combination with bevacizumab compared with irinotecan /5FU/FA alone. Due to high inter-patient variability and limited sampling, it is uncertain if the increase in SN-38 levels observed was due to bevacizumab. There was a small increase in diarrhoea and

leukopenia adverse events. More dose reductions of irinotecan were reported for patients receiving irinotecan /5FU/FA in combination with bevacizumab.

Patients who develop severe diarrhoea, leukopenia, or neutropenia with the bevacizumab and irinotecan combination should have irinotecan dose modifications as specified in section 4.2 Posology and method of administration.

4.6 Pregnancy and lactation

III.3.8.12 Pregnancy

There is no information on the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic, foetotoxic and teratogenic in rabbits and rats. Therefore, Irinotecan Actavis must not be used during pregnancy (see section 4.3 and section 4.4).

III.3.8.13 Women of child-bearing potential

Women of child-bearing age receiving Irinotecan Actavis should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur (see section 4.3 and section 4.4).
Contraceptive measures must be taken by women of child-bearing age, and also by male patients, during and for at least three months after cessation of therapy.

III.3.8.14 Lactation

In lactating rats, ^{14}C-irinotecan was detected in milk. It is not known whether irinotecan is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding must be discontinued for the duration of irinotecan therapy (see section 4.3).

III.3.8.14.1 4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur.

III.3.8.14.2 4.8 Undesirable effects

Undesirable effects detailed in this section refer to irinotecan. There is no evidence that the safety profile of irinotecan is influenced by cetuximab or *vice versa*. In combination with cetuximab, additional reported undesirable effects were those expected with cetuximab (such as acneform rash 88%). Therefore also refer to the product information of cetuximab.

For information on adverse reactions in combination with bevacizumab, refer to the bevacizumab summary product of characteristics.

The following adverse reactions considered to be possibly or probably related to the administration of irinotecan hydrochloride trihydrate have been reported from 765 patients at the recommended dose of 350 mg/m² in monotherapy, and from 145 patients treated by irinotecan hydrochloride trihydrate in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m².

Frequency estimate: Very Common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000)

III.3.9 Gastrointestinal disorders

III.3.9.1 Delayed diarrhoea

Diarrhoea (occurring more than 24 hours after administration) is a dose-limiting toxicity of Irinotecan Actavis. *In monotherapy*:
Very Common: Severe diarrhoea was observed in 20 % of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14 % have severe diarrhoea. The median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan hydrochloride trihydrate. *In combination therapy:*
Very Common: Severe diarrhoea was observed in 13.1 % of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9 % have severe diarrhoea.

Uncommon:
Cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically (*Clostridium difficile*).

Nausea and vomiting In monotherapy:
Very Common: Nausea and vomiting were severe in approximately 10 % of patients treated with antiemetics.
In combination therapy:
Common: A lower incidence of severe nausea and vomiting was observed (2.1 % and 2.8 % of patients respectively).

III.3.9.2 Dehydration

Common: Episodes of dehydration associated with diarrhoea and/or vomiting.

Uncommon: Cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting.

III.3.9.3 Other gastrointestinal disorders

Common: Constipation relative to irinotecan and/or loperamide has been observed, shared between :
• in monotherapy : in less than 10% of patients • in combination therapy : 3.4% of patients.

Uncommon: Intestinal obstruction, ileus, or gastrointestinal haemorrhage Rare:
Colitis, including typhlitis, ischemic and ulcerative colitis and intestinal perforation.
Cases of symptomatic or asymptomatic pancreatitis have been associated with irinotecan therapy.
Other mild effects include anorexia, abdominal pain and mucositis.

III.3.10 Blood and lymphatic system disorders

Neutropenia is a dose-limiting toxic effect. Neutropenia was reversible and not cumulative; the median day to nadir was 8 days whatever the use in monotherapy or in combination therapy.

In monotherapy:
Very Common: Neutropenia was observed in 78.7% of patients and was severe (neutrophil count <500 cells/mm^3) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil

count below 1,000 cells/mm³ including 7.6% with a neutrophil count <500 cells/mm³. Total recovery was usually reached by day 22.
Anaemia was reported in about 58.7% of patients (8% with haemoglobin <80 g/l and 0.9% with haemoglobin <65 g/l).

Common: Fever with severe neutropenia was reported in 6.2% of patients and in 1.7% of cycles. Infectious episodes occurred in about 10.3% of patients (2.5% of cycles) and were associated with severe neutropenia in about 5.3% of patients (1.1% of cycles), and resulted in death in 2 cases.
Thrombocytopenia (< 100,000 cells/mm³) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelets count ≤ 50,000 cells/mm^3 and 0.2% of cycles. Nearly all the patients showed a recovery by day 22.

In combination therapy:
Very Common: Neutropenia was observed in 82.5% of patients and was severe (neutrophil count <500 cells/mm^3) in 9.8 % of patients. Of the evaluable cycles, 67.3 % had a neutrophil count below 1,000 cells/mm³ including 2.7% with a neutrophil count <500 cells/mm³. Total recovery was usually reached within 7-8 days.
Anaemia was reported in 97.2% of patients (2.1% with haemoglobin <80 g/l).
Thrombocytopenia (<100,000 cells/mm³) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (<50,000 cells/mm³) has been observed. One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.

Common: Fever with severe neutropenia was reported in 3.4% of patients and in 0.9% of cycles.

Infectious episodes occurred in about 2% of patients (0.5% of cycles) and were associated with severe neutropenia in about 2.1% of patients (0.5% of cycles), and resulted in death in 1 case.

III.3.11 Infections and Infestations

Uncommon: Renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced sepsis.

III.3.12 General disorders and administration site conditions

III.3.12.1Acute cholinergic syndrome

Common: Severe transient acute cholinergic syndrome was observed in 9% of patients treated in monotherapy and in 1.4% of patients treated in combination therapy. The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lachrimation and increased salivation occurring during or within the first 24 hours after the infusion of irinotecan hydrochloride trihydrate. These symptoms disappear after atropine administration (see section 4.4).

Asthenia was severe in less than 10% of patients treated in monotherapy and in 6.2% of patients treated in combination therapy. The causal relationship to irinotecan has not been clearly established.

Fever in the absence of infection and without concomitant severe neutropenia, occurred in 12% of patients treated in monotherapy and in 6.2% of patients treated in combination therapy.

Uncommon: Mild infusion site reactions have been reported.

Cardiac disorders
Rare: Hypertension during or following the infusion.

III.3.13 Respiratory, thoracic and mediastinal disorders
Uncommon: Interstitial pulmonary disease presenting as pulmonary infiltrates. Early effects such as dyspnoea have been reported (see section 4.4).

III.3.14 Skin and subcutaneous tissue disorders
Very common: Reversible alopecia.
Uncommon: Mild cutaneous reactions.

III.3.15 Immune system disorders
Uncommon: Mild allergy reactions
Rare: Anaphylactic/anaphylactoid reactions.

III.3.16 Musculoskeletal and connective tissue disorders
Rare: Early effects such as muscular contraction or cramps and paresthesia have been reported.

III.3.17 Investigations
Very Common: In combination therapy transient serum levels (grades 1 and 2) of either ALT (alanine aminotransferase) , AST (aspartate aminotransferase) , alkaline phosphatase or bilirubin were observed in 15%, 11%, 11% and 10% of the patients, respectively, in the absence of progressive liver metastasis. Transient grade 3 were observed in 0%, 0%, 0% and 1% of the patients, respectively. No grade 4 was observed.

Common: In monotherapy, transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in 9.2%, 8.1% and 1.8% of the patients, respectively, in the absence of progressive liver metastasis. Transient and mild to moderate increases of serum levels of creatinine have been observed in 7.3% of the patients.
Rare: Hypokalemia and hyponatremia mostly related with diarrhea and vomiting.

Very Rare: Increases of amylase and/or lipase.

III.3.18 Nervous system disorders
Very rare::Transient speech disorders associated with infusion of irinotecan.

III.3.18.14.9 Overdose
There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea. There is no known antidote for irinotecan. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

III.4 5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antinetoplastic agents, ATC Code: L01XX19.

III.4.1 Experimental data

Irinotecan is a semi-synthetic derivative of camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found time-dependent and was specific to the S phase.

In vitro, irinotecan and SN-38 were not found to be significantly recognised by the Pglycoprotein MDR, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines.

Furthermore, irinotecan has a broad antitumor activity *in vivo* against murine tumour models (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinomas) and against human xenografts (Co-4 colon adenocarcinoma, Mx-1 mammary adenocarcinoma, ST-15 and SC-16 gastric adenocarcinomas). Irinotecan is also active against tumors expressing the Pglycoprotein MDR (vincristine- and doxorubicin-resistant P388 leukaemia's).

Beside the antitumor activity of irinotecan, the most relevant pharmacological effect is the inhibition of acetylcholinesterase.

III.4.2 Clinical data

In monotherapy: Clinical phase II/III studies were performed in more than 980 patients in the every 3 week dosage schedule with metastatic colorectal cancer who failed a previous 5-FU regimen. The efficacy of irinotecan was evaluated in 765 patients with documented progression on 5-FU at study entry.

	Phase III					
	Irinotecan versus supportive care			**Irinotecan versus 5FU**		
	Irinotecan hydrochloride trihydrate *n=183*	*Supportive care* *n=90*	*p values*	*Irinotecan hydrochloride trihydrate* *n=127*	*5FU* *n=129*	*p values*

Progression Free Survival at 6 months (%)	NA	NA		33.5*)	26.7	p=0.03
Survival at 12 months (%)	36.2*)	13.8	p=0.0001	44.8*)	32.4	p=0.0351
Median survival (months)	9.2*)	6.5	p=0.0001	10.8*)	8.5	p=0.0351

NA: Non Applicable

*) : Statistically significant difference

In phase II studies, performed on 455 patients in the every 3-week dosage schedule, the progression free survival at 6 months was 30% and the median survival was 9 months. The median time to progression was 18 weeks.

Additionally, non-comparative phase II studies were performed in 304 patients treated with a weekly schedule regimen, at a dose of 125 mg/m² administered as an intravenous infusion over 90 minutes for 4 consecutive weeks followed by 2 weeks rest. In these studies, the median time to progression was 17 weeks and median survival was 10 months. A similar safety profile has been observed in the weeklydosage schedule in 193 patients at the starting dose of 125 mg/m², compared to the every 3-week-dosage schedule. The median time of onset of the first liquid stool was on day 11.

In combination therapy: A phase III study was performed in 385 previously untreated metastatic colorectal cancer patients treated with either every 2 weeks schedule (see section 4.2) or weekly schedule regimens. In the every 2 weeks schedule, on day 1, the administration of irinotecan hydrochloride trihydrate at 180 mg/m² once every 2 weeks is followed by infusion with folinic acid (200 mg/m² over a 2-hour intravenous infusion) and 5-fluorouracil (400 mg/m² as an intravenous bolus, followed by 600 mg/m² over a 22-hour intravenous infusion). On day 2, folinic acid and 5-fluorouracil are administered at the same doses and schedules. In the weekly schedule, the administration of irinotecan hydrochloride trihydrate at 80 mg/m² is followed by infusion with folinic acid (500 mg/m² over a 2-hour intravenous infusion) and then by 5-fluorouracil (2300 mg/m² over a 24-hour intravenous infusion) over 6 weeks. In the combination therapy trial with the 2 regimens described above, the efficacy of irinotecan was evaluated in 198 treated patients:

	Combined regimens (n=198)		**Weekly schedule (n=50)**		**Every 2 weeks schedule (n=148)**	
	Irinotecan hydrochloride trihydrate +5FU/FA	5FU/FA	Irinotecan hydrochloride trihydrate +5FU/FA	5FU/FA	Irinotecan hydrochloride trihydrate +5FU/FA	5FU/FA

Response rate (%)	40.8*)	23.1*)	51.2*)	28.6*)	37.5*)	21.6*)
p value	p<0.001		p=0.045		p=0.005	
Median time to progression (months)	6.7	4.4	7.2	6.5	6.5	3.7
p value	p<0.001		NS		p=0.001	
Median duration of response (months)	9.3	8.8	8.9	6.7	9.3	9.5
p value	NS		p=0.043		NS	
Median duration of response and stabilisation (months)	8.6	6.2	8.3	6.7	8.5	5.6
p value	p<0.001		NS		p=0.003	
Median time to treatment failure (months)	5.3	3.8	5.4	5.0	5.1	3.0
p value	p=0.0014		NS		P<0.001	
Median survival (months)	16.8	14.0	19.2	14.1	15.6	13.0
p value	p=0.028		NS		p=0.041	

5FU : 5-fluorouracil
FA : folinic acid
NS : Non Significant
*): As per protocol population analysis

In the weekly schedule, the incidence of severe diarrhoea was 44.4% in patients treated by irinotecan in combination with 5FU/FA and 25.6% in patients treated by 5FU/FA alone. The incidence of severe neutropenia (neutrophil count <500 cells/mm^3) was 5.8% in patients treated by irinotecan in combination with 5FU/FA and in 2.4% in patients treated by 5FU/FA alone.

Additionally, median time to definitive performance status deterioration was significantly longer in irinotecan combination group than in 5FU/FA alone group (p=0.046).

Quality of life was assessed in this phase III study using the EORTC QLQ-C30 questionnaire. Time to definitive deterioration constantly occurred later in the irinotecan groups. The evolution of the Global Health Status/Quality of life was slightly better in irinotecan combination group although not significant, showing that efficacy of irinotecan in combination could be reached without affecting the quality of life.

In combination with cetuximab:

The efficacy of the combination of cetuximab with irinotecan was investigated in two clinical studies. A total of 356 patients with EGFR-expressing metastatic colorectal cancer who had recently failed irinotecan including cytotoxic therapy and who had a minimum Karnofsky performance status of 60, but the majority of whom had a Karnofsky performance status of ≥80 received the combination treatment. EMR 62 202-007: This randomised study compared the combination of cetuximab and irinotecan (218 patients) with cetuximab monotherapy (111 patients). IMCL CP02-9923: This single arm open-label study investigated the combination therapy in 138 patients.
The efficacy data from these studies are summarised in the table below:

Study	**N**	**ORR**		**DCR**		**PFS (months)**		**OS (months)**	
		n (%)	**95%CI**	**n (%)**	**95%CI**	**Median**	**95%CI**	**Median**	**95%CI**
Cetuximab + irinotecan									
EMR 62 202-007	218	50 (22.9)	17.5, 29.1	121 (55.5)	48.6, 62.2	4.1	2.8, 4.3	8.6	7.6, 9.6
IMCL CP02-9923	138	21 (15.2)	9.7, 22.3	84 (60.9)	52.2, 69.1	2.9	2.6, 4.1	8.4	7.2, 10.3
Cetuximab									
EMR 62 202-007	111	12 (10.8)	5.7, 18.1	36 (32.4)	23.9, 42.0	1.5	1.4, 2.0	6.9	5.6, 9.1

CI = confidence interval, DCR = disease control rate (patients with complete response, partial response, or stable disease for at least 6 weeks), ORR = objective response rate (patients with complete response or partial response), OS = overall survival time, PFS = progression-free survival.
The efficacy of the combination of cetuximab with irinotecan was superior to that of Cetuximab monotherapy, in terms of objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). In the randomised trial, no effects on overall survival were demonstrated (hazard ratio 0.91, p = 0.48).

In combination with bevacizumab:
A phase III randomised, double-blind, active-controlled clinical trial evaluated bevacizumab in combination with irinotecan /5FU/FA as first-line treatment for metastatic carcinoma of the colon or rectum (Study AVF2107g). The addition of bevacizumab to the combination of irinotecan /5FU/FA resulted in a statistically significant increase in overall survival. The

clinical benefit, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease. Refer also to the bevacizumab summary of product characteristics. The efficacy results of Study AVF2107g are summarized in the table below.

	AVF2107g	
	Arm 1 irinotecan **/5FU/FA □□Placebo**	**Arm 2** irinotecan **/5FU/FA □□Avastin[a]**
Number of Patients	411	402
Overall survival		
Median time (months)	15.6	20.3
95% Confidence Interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]		0.660
p-value		0.00004
Progression-free survival		
Median time (months)	6.2	10.6
Hazard ratio		0.54
p-value		□0.0001
Overall response rate		
Rate (%)	34.8	44.8
95% CI	30.2 – 39.6	39.9 – 49.8
p-value		0.0036
Duration of response		
Median time (months)	7.1	10.4
25–75 percentile (months)	4.7 – 11.8	6.7 – 15.0

[a] 5 mg/kg every 2 weeks. [b] Relative to control arm.

III.4.3 Pharmacokinetic/Pharmacodynamic data

The intensity of the major toxicities encountered with irinotecan (e.g., leukoneutropenia and diarrhoea) are related to the exposure (AUC) to parent drug and metabolite SN-38. Significant correlations were observed between haematological toxicity (decrease in white blood cells and neutrophils at nadir) or diarrhoea intensity and both irinotecan and metabolite SN-38 AUC values in monotherapy.

III.4.3.1 5.2 Pharmacokinetic properties

In a phase I study in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 to 750 mg/m² every three weeks, irinotecan showed a biphasic or triphasic elimination profile. The mean plasma clearance was 15 L/h/m² and the volume of distribution at steady state (Vss): 157 L/m². The mean plasma half-life of the first phase of the triphasic model was 12 minutes, of the second phase 2.5 hours, and the terminal phase half-life was 14.2 hours. SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13.8 hours. At the end of the infusion, at the recommended dose of 350 mg/m², the mean peak plasma concentrations of irinotecan and SN-38 were 7.7 µg/ml and 56 ng/ml, respectively, and the mean area under the curve (AUC) values were 34 µg.h/ml and 451

ng.h/ml, respectively. A large interindividual variability in pharmacokinetic parameters is generally observed for SN-38.

A population pharmacokinetic analysis of irinotecan has been performed in 148 patients with metastatic colorectal cancer, treated with various schedules and at different doses in phase II trials. Pharmacokinetic parameters estimated with a three compartment model were similar to those observed in phase I studies. All studies have shown that irinotecan (CPT-11) and SN-38 exposure increase proportionally with CPT-11 administered dose; their pharmacokinetics are independent of the number of previous cycles and of the administration schedule.

In vitro, plasma protein binding for irinotecan and SN-38 was approximately 65 % and 95 % respectively.

Mass balance and metabolism studies with 14 C-labelled drug have shown that more than 50% of an intravenously administered dose of irinotecan is excreted as unchanged drug, with 33% in the faeces mainly via the bile and 22% in urine.

Two metabolic pathways account each for at least 12% of the dose:

- Hydrolysis by carboxylesterase into active metabolite SN-38. SN-38 is mainly eliminated by glucuronidation, and further by biliary and renal excretion (less than 0.5% of the irinotecan dose) The SN-38 glucuronite is subsequently probably hydrolysed in the intestine.
- Cytochrome P450 3A enzymes-dependent oxidations resulting in opening of the outer piperidine ring with formation of APC (aminopentanoic acid derivate) and NPC (primary amine derivate) (see section 4.5).

Unchanged irinotecan is the major entity in plasma, followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity.

Irinotecan clearance is decreased by about 40% in patients with bilirubinemia between 1.5 and 3 times the ULN. In these patients a 200 mg/m² irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m² in cancer patients with normal liver parameters.

III.4.3.2 5.3 Preclinical safety data

Irinotecan and SN-38 have been shown to be mutagenic *in vitro* in the chromosomal aberration test on CHO-cells as well as in the *in vivo* micronucleus test in mice. However, they have been shown to be devoid of any mutagenic potential in the Ames test.

In rats treated once a week during 13 weeks at the maximum dose of 150 mg/m² (which is less than half the human recommended dose), no treatment related tumours were reported 91 weeks after the end of treatment.

Single- and repeated-dose toxicity studies with irinotecan have been carried out in mice, rats and dogs. The main toxic effects were seen in the haematopoietic and lymphatic systems. In dogs, delayed diarrhoea associated with atrophy and focal necrosis of the intestinal mucosa was reported. Alopecia was also observed in the dog. The severity of these effects was dose-related and reversible.

III.5 6 PHARMACEUTICAL PARTICULARS

III.5.1 6.1 List of excipients

Sorbitol E420
Lactic Acid
Sodium Hydroxide (to pH 3.5)
Water for injection

III.5.2 6.2 Incompatibilities

Irinotecan Actavis must not be mixed with other medicinal products, except those mentioned in section 6.6 (see also section 4.2).

6.3 Shelf life

Vial before opening
2 years.

After opening
The content of the vial should be used immediately after the first breakage of vial.

III.5.3 After dilution
Chemical and physical in-use stability of the drug product after dilution in the recommended solutions for infusion (see section 6.6) has been demonstrated for 24 hours at 30°C and for 48 hours at 2-8°C.
From a microbiological point of view, unless the methods of opening and dilution preclude the risk of microbial contamination, the product should be used immediately after dilution.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

III.5.3.1 6.4 Special precautions for storage

Store in the original package in order to protect from light.
Do not freeze.
For storage conditions of the diluted medicinal product, see section 6.3.

III.5.3.2 6.5 Nature and contents of container

Brown glass vial (type I) with bromobutylic rubber stopper and metallic cap (aluminium) with polypropylene disk. Vial will be packed with or without a protective plastic overwrap.

III.5.4 Pack sizes
1 x 2 ml vial
1 x 5 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

III.5.5 Handling
As with all antineoplastic agents, caution should be exercised when handling Irinotecan Actavis. 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.

III.5.6 Instructions for dilution

Irinotecan Actavis 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 Actavis 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 procedures for cytotoxic agents.

Protection instructions for preparation of Irinotecan Actavis 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 amounts 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 Actavis 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 a doctor.

5. In case of contact of Irinotecan Actavis with eyes, wash them thoroughly with plenty of water. Contact an ophthalmologist immediately.

III.5.7 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.

III.6 7 MARKETING AUTHORISATION HOLDER

Actavis Group hf.
Reykjavíkurvegi 76-78
IS-220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER(S)

PL21231/0024

III.7 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/11/2007

10 DATE OF REVISION OF THE TEXT

21/11/2007

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

IV. MODULE 3

IV.1 PACKAGE LEAFLET: INFORMATION FOR THE USER

Irinotecan Actavis 20 mg/ml concentrate for solution for infusion
Irinotecan hydrochloride trihydrate

Read all of this leaflet carefully before you start using this medicine.
- **Keep this leaflet. You may need to read it again.**
- **If you have any further questions, ask your doctor.**
- **This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.**
- **If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.**

In this leaflet:

1. What Irinotecan is and what it is used for
2. Before you use Irinotecan
3. How to use Irinotecan
4. Possible side effects
5. How to store Irinotecan
6. Further information

1. What Irinotecan is and what it is used for
Irinotecan belongs to a group of medicines called cytostatics (anti-cancer medicines).
Irinotecan is used for the treatment of advanced cancer of the colon and rectum in adults, either in a combination with other medicines or alone.

2. Before you use Irinotecan

Do not use Irinotecan if you
- are allergic (hypersensitive) to irinotecan hydrochloride trihydrate or any of the other ingredients of Irinotecan
- have any other bowel disease or a history of bowel obstruction
- are pregnant or breast feeding
- have increased levels of bilirubin in the blood (more than 3 times the upper limit of normal)
- have severe bone marrow failure
- are in a poor general health (evaluated by an international standard)
- are using the natural remedy St Johns' Wort *(Hypericum perforatum)*

Take special care with Irinotecan
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 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 may help you to remember that.

1) The first 24 hours after administration of Irinotecan
During administration of Irinotecan (30-90 min.) and shortly 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.

2) From the day after treatment with Irinotecan until next treatment
During this period 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 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 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.
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 unit at the hospital supervising the Irinotecan treatment. It is very important that they are aware of the diarrhoea.

You must immediately tell the doctor, or the unit supervising the treatment, if
- **you have nausea, vomiting or any fever as well as diarrhoea**
- **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 anti-diarrhoeal treatment should **not** be used to prevent a further episode of diarrhoea, 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 and vomiting
If you have nausea and/or vomiting contact your doctor or the 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 the liver function should be monitored (by blood tests).

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.

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.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is also valid for herbal medicines, strong vitamins and minerals.
Some medicines may alter the effects of Irinotecan e.g. ketoconazole (for the treatment of fungal infections), rifampicin (for the treatment of tuberculosis) and some medicines for the treatment of epilepsy (carbamazepine, phenobarbital and phenytoin).
The herbal medicine St John's Wort *(Hypericum perforatum)* may not be used concurrent with Irinotecan and not between treatments, as it may decrease the effect of irinotecan.
If you require an operation, please tell your doctor or anaesthetist that you are using this medicine, as it may alter the affect of some medicines used during surgery.

Pregnancy and breast-feeding
Irinotecan must not be used during pregnancy.
Women of child-bearing age should avoid becoming pregnant. Contraceptive measures must be taken by both male and female patients during and for at least three months after cessation of therapy. Still, if you become pregnant during this period you must

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Irinotecan Actavis 20 mg/ml concentrate for solution for infusion
Irinotecan hydrochloride trihydrate

The following information is intended for medical or healthcare professionals only:

Instruction for use - Cytotoxic

Handling of Irinotecan
As with all antineoplastic 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 amounts of cold water
   - the flushed surfaces should then be wiped thoroughly

immediately inform your doctor.
Breast-feeding must be discontinued for the duration of irinotecan therapy.

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 use any tools or machines.

Important information about some of the ingredients of Irinotecan
Irinotecan contains **sorbitol.** If you suffer from an **intolerance to some sugars,** tell your doctor before you are given this medicinal product.

3. How to use Irinotecan

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, size 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 (m2).

- If you have previously been treated with 5-fluorouracil you will normally be treated with Irinotecan alone starting with a dose of 350 mg/m2 every 3 weeks.
- If you have not had previous chemotherapy you will normally receive 180 mg/m2 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.

4. Possible side effects

Like all medicines, Irinotecan 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, see also information in section "Take special care with Irinotecan ".

Very common side effects (more than 1 in 10 patients):
- Blood disorders: Neutropenia (decreased number of some white blood cells), thrombocytopenia (decreased number of blood platelets), anaemia.
- Delayed diarrhoea.
- Nausea, vomiting.
- Hair loss (the hair grows again after end of treatment).
- In combination therapy transient serum levels of some enzymes (ALT, AST, alkaline phosphatase) or bilirubin

Common side effects (less than 1 in 10 patients):
- 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; widening of the blood vessels; 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 .
- Fever, infections.
- Fever associated with a severe decrease in the number of some white blood cells
- Dehydration, commonly associated with diarrhoea and /or vomiting.
- Constipation.
- Fatigue.
- Increased levels of liver enzymes and creatinine in the blood

Uncommon side effects (Less than 1 in 100 patients):
- Allergic reactions.
- Mild skin reactions; mild reactions at the infusion site.
- Early effects such as breathing difficulties.
- Lung disease (interstitial pulmonary disease).
- Intestinal blockage.
- Abdominal pain and inflammation, causing diarrhoea (a condition known as pseudomembraneous colitis)
- Infrequent cases of renal insufficiency, low blood pressure or cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting or sepsis.

Rare side effects (Less than 1 in 1000 patients):
- Severe allergic reactions (anaphylactic/anaphylactoid reactions). If this happens you should tell your doctor immediately
- Early effects such as muscular contraction or cramps and numbness (paraesthesia).
- Gastrointestinal bleeding and inflammation of the colon including the appendix.
- Intestinal perforation; Anorexia; abdominal pain; inflammation of the mucous membranes.
- Inflammation of the pancreas.
- Increased blood pressure during and following administration.
- Decreased levels of potassium and sodium in the blood, mostly related to diarrhoea and vomiting.

Very rare side effects (Less than 1 in 10,000 patients)
- Transient speech disorders.
- Increase in levels of some digestive enzymes which break down sugars and fats

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Irinotecan

Keep out of the reach and sight of children.
Do not freeze.
For single use only.
Keep the vial in the outer carton in order to protect from light.
Do not use this medicinal product after the expiry date which is stated on the carton 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 temperatures up to 30°C and for 48 hours at 2-8°C (e.g. in a fridge).
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose medicines no longer required. These measures will help to protect the environment

6. Further information

What Irinotecan 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 2ml vial contains 40 mg irinotecan hydrochloride trihydrate.
- One 5ml vial contains 100 mg irinotecan hydrochloride trihydrate.
- The other ingredients are sorbitol E420, lactic acid, sodium hydroxide and water for injections

What Irinotecan looks like and contents of the pack
Irinotecan 20 mg/ml concentrate for solution for infusion is a clear, colourless to slightly yellow solution.

Pack size:
1 x 2 ml vial or 1 x 5 ml vial

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Actavis Group hf.
Reykjavikurvegi 76-78,
IS-220 Hafnarfjörður
Iceland

Manufacturer
Actavis Nordic A/S
Ørnegårdsvej 16
DK-2820 Gentofte
Denmark
Or
S.C. SINDAN- PHARMA S.R.L.
11 Ion Mihalache Blvd,
011171 Bucharest, Romania

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

Austria:	Irinotecan Actavis 20mg/ml, Konzentrat zur Herstellung einer Infusionslösung
Belgium:	IRINOTECAN ACTAVIS GROUP 20mg/ml, solution à diluer pour perfusion
Germany:	Irinotecan-Actavis 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung
France:	IRINOTECAN ACTAVIS 20mg/ml, solution à diluer pour perfusion
Ireland:	Irinotecan hydrochloride 20mg/ml Concentrate for solution for infusion;
Malta:	Irinotecan Actavis 20mg/ml Concentrate for solution for infusion
Portugal:	Irinotecano Actavis
Spain:	Irinotecan Actavis 20mg/ml concentrado para solución para perfusión
Czech, Slovakia: Denmark, Estonia, Finland, Iceland, Italy, Lithuania, Latvia, Netherlands,	Irinotecan HCL Actavis 20 mg/ml
Norway, Sweden: Hungary, Poland, Slovenia:	Irinotecan Actavis Irinotesin

This leaflet was last approved in (MM/YYYY).

Actavis, Barnstaple, EX32 8NS, UK

SINPL002

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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 a doctor.
5. In case of contact of Irinotecan with eyes, wash them thoroughly with plenty of water. Contact an ophthalmologist immediately.

Preparation of 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 procedures 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.

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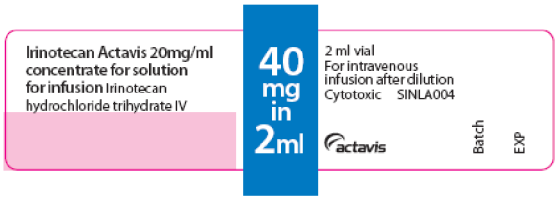
V. MODULE 4 LABELLING

Carton- 2ml vial



Carton- 5ml vial

VI. MODULE 5 SCIENTIFIC DISCUSSION DURING INITIAL PROCEDURE

VI.1 I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Irinotecan Actavis, in the treatment of advanced colorectal cancer, is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended, Irinotecan Hydrochloride Trihydrate 20mg/ml Concentrate for Solution for Infusion, has been shown to be a generic product of

Campto 20mg/ml (concentrate for solution for infusion) which was granted to Pfizer Holding France, on 5th May 1995, over 10 years ago.

Irinotecan, a Camptothecin, is licensed for first-line use in patients with advanced or metastatic colorectal cancer (in combination with fluorouracil and folinic acid) or as secondline monotherapy when fluorouracil-based therapy has failed. Irinotecan is administered intravenously at doses ranging from 180-350 mg/m^2 over a 30-90 minute period. Irinotecan is metabolized to SN-38 in the presence of hepatic or gastrointestinal carboxylesterases. SN-38 is 100-1000 fold more cytotoxic than Irinotecan. Irinotecan and SN-38 form a cleavable drug-topoisomerase I-DNA complex, which results in lethal double stranded DNA breaks. DNA strand breaks lead to activation of apoptosis and cell death. Diarrhoea is the most common adverse event and may cause life threatening hypovolaemia in severe late onset cases. Myelosuppression (neutropenia) is also a frequent dose-limiting adverse event and septic deaths have been reported.

The drug product Irinotecan Actavis corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitive compostion in terms of active substance (20 mg Irinotecan hydrochloride/ ml) and the same dosage form (Concentrate for solution for infusion). The proposed product is developed using an approved drug substance which is to be administered as an aqueous intravenous solution containing the same drug substance in the same concentration. Therefore a bioequivalence study is not required in support of this application.

No new preclinical or clinical studies were conducted and none are required for an application of this type. This application for a generic product refers to Campto 20mg/ml (concentrate for solution for infusion) (Pfizer Holding France) which has been licensed within the EEA for over 10 years

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

User testing was performed in English and resulted in a 96.1% score for understanding and 94.7% score for locating the information. The criteria for a successful test was fulfilled (>80%) and therefore the test was deemed satisfactory.

VI.2 II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Irinotecan Actavis 20mg/ml- concentrate for solution for infusion.
Name(s) of the active substance(s) (INN)	Irinotecan Hydrochloride Trihydrate
Pharmacotherapeutic classification (ATC code)	Cytostatic topoisomerase I inhibitor (L01XX19)
Pharmaceutical form and strength(s)	20mg/ml concentrate for solution for infusion
Reference numbers for the Mutual Recognition Procedure	UK/H/1013/001/DC

Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Norway, Poland, Portugal, Slovenia, Slovak Republic, Spain and Sweden
Marketing Authorisation Number(s)	PL 21231/0024
Name and address of the authorisation holder	Actavis Group hf, Reykjavikurvegi 76-78, Hafnarfjordur, IS-220, Iceland

VI.3 III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

VI.3.1 S. Active substance

The chemical-pharmaceutical documentation and Expert Report in relation to Irinotecan Actavis are of sufficient quality in view of the present European regulatory requirements. The active substance irinotecan hydrochloride trihydrate is not reported in any international pharmacopoeia. The drug substance specification for drug substance is generally acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 12 months is acceptable.

VI.3.2 P Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three commercial batches of 40mg/2ml and 100mg/5ml presentation. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 24 months is acceptable.

VI.3.3 III.2 PRE-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of irinotecan hydrochloride trihydrate are well known. As irinotecan hydrochloride trihydrate is a widely used, well known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a critical appraisal of the relevant literature that dates from 1990 to 2004 has been provided and is adequate. There are no objections to approval of Irinotectan Actavis from a non-clinical point of view.

VI.3.4 III.3 CLINICAL ASPECTS Bioequivalence studies

No new data have been submitted and none are required for this application. According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

VI.3.5 Pharmacodynamics

No novel pharmacodynamic data are supplied or required for this application. The pharmacodynamic claims in the SPC are appropriately consistent with the innovator product.

VI.3.6 Clinical efficacy

No novel efficacy data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the efficacy of Irinotecan. The clinical overview describes several clinical trials which have established Irinotecan as one of the most active drugs in first and second line treatment of colorectal cancer. Irinotecan has an acceptable adverse events profile (Rothenberg et al., 2001, Kohne et al., 2005, Falcone et al., 2001, Vanhoefer et al., 2001, Saltz et al., 2001, Douillard et al., 2000, Teufel et al., 2004, Rothenberg et al., 1999, Rougier et al., 1998).

VI.3.7 Clinical safety

No novel safety data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the safety of irinotecan hydrochloride trihydrate. No new safety data have been identified.

VI.4 IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Irinotectan Actavis are well-defined and controlled.
The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new preclinical data were submitted and none are required for an application of this type.

No bioequivalence data were submitted and none are required for an application of this type.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with irinotecan hydrochloride trihydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.