Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Irinotecan HCl AqVida 20 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The concentrate contains 20 mg/ml irinotecan hydrochloride 3 H_2O (equivalent to 17.33 mg/ml irinotecan). The irinotecan vials contain 40 mg, 100 mg, 300 mg or 500 mg irinotecan hydrochloride 3 H_2O.

Excipient with known effect
This medicinal product contains 45 mg sorbitol per ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Pale yellow, clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- In combination with 5-fluorouracil and folinic acid in patients who have not undergone a previous chemotherapy for the treatment of the advanced cancer,
- As monotherapy in patients who have not responded to previous treatment with an established regimen containing 5-fluorouracil.

Irinotecan in combination with cetuximab is indicated for the treatment of patients with metastatic KRAS wild-type colorectal cancer expressing the epidermal growth factor receptor (EGFR) who have not received prior treatment for the metastatic disease or after failure of a cytotoxic therapy that included irinotecan (see section 5.1).

Irinotecan in combination with 5-fluorouracil, folinic acid and bevacizumab is indicated for first-line treatment of patients with metastatic colorectal cancer.

Irinotecan in combination with capecitabine with or without bevacizumab is indicated for first-line treatment of patients with metastatic colorectal cancer.

4.2 Posology and method of administration

Only for adults. Irinotecan solution for infusion is infused into a peripheral or central vein.

It should not be given as an intravenous bolus or as an intravenous infusion lasting less than 30 minutes or more than 90 minutes.

Posology

As monotherapy (for previously treated patients):

The recommended dose for irinotecan hydrochloride 3 H_2O is 350 mg/m^2 of body surface area (BSA) and is given as an intravenous infusion over 30 to 90 minutes every 3 weeks (see sections 4.4 and 6.6).

As combination therapy (for patients who have not been previously treated):

The safety and efficacy of irinotecan hydrochloride 3 H_2O in combination with 5-fluorouracil (5-FU) and folinic acid (FA) have been evaluated as per the following regimen (see section 5.1):

- Irinotecan plus 5-fluorouracil and folinic acid every 2 weeks

The recommended dose for irinotecan hydrochloride 3 H_2O is 180 mg/m^2 of body surface area once every 2 weeks, administered as intravenous infusion over 30–90 minutes, followed by an infusion of folinic acid and 5-fluorouracil.

For the dosage and method of administration of cetuximab, please refer to the Summary of Product Characteristics for cetuximab.

Usually, the same dose of irinotecan is used as that administered over the last cycles of the previous regimen containing irinotecan. Irinotecan must not be given earlier than 1 hour after the end of the cetuximab infusion.

For the dosage and method of administration of bevacizumab, please refer to the Summary of Product Characteristics for bevacizumab.

For the dosage and method of administration in combination with capecitabine, see section 5.1 and the relevant paragraphs of the Summary of Product Characteristics for capecitabine.

Dose adjustment

Irinotecan must not be administered until after appropriate recovery from all grade 0 or 1 undesirable effects according to the NCI-CTC (National Cancer Institute Common Toxicity Criteria) and after treatment-related diarrhoea has fully resolved.

At the beginning of a subsequent therapy cycle, the dose of irinotecan and 5-FU, where applicable, must be reduced according to the worst degree of undesirable effects observed over the previous therapy cycle. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related undesirable effects.

If the following undesirable effects occur, the irinotecan and/or 5-FU dose should be reduced by 15 to 20 %:

- haematological toxicity: grade 4 neutropenia, febrile neutropenia (grade 3–4 neutropenia and grade 2–4 fever), thrombocytopenia and leukopenia (grade 4);
- non-haematological toxicity (grade 3–4).

The recommendations for cetuximab dose adjustment when administered in combination with irinotecan according to the Summary of Product Characteristics for cetuximab should be followed.

For dose adjustment of bevacizumab when administered in combination with irinotecan/5-FU/FA, please refer to the Summary of Product Characteristics for bevacizumab.

If used in combination with capecitabine in patients aged 65 years or more, it is recommended to reduce the starting dose of capecitabine to 800 mg/m^2 twice daily as per the Summary of Product

Characteristics for capecitabine. See also the dose adjustment recommendations for use as combination therapy provided in the Summary of Product Characteristics for capecitabine.

Treatment duration

Treatment with irinotecan should be continued until objective disease progression or unacceptable toxicity occurs.

Particular patient groups:

Patients with impaired hepatic function

Monotherapy
In patients with a performance status ≤ 2, the starting dose of irinotecan is based on blood bilirubin levels [up to 3 times the upper limit of normal (ULN)]. In these patients with hyperbilirubinaemia and a prothrombin time greater than 50%, clearance of irinotecan is reduced (see section 5.2), increasing the risk of hematotoxicity. Therefore, weekly complete blood count monitoring should be conducted in this patient population.

- In patients with bilirubin levels up to 1.5 times ULN, the recommended dose of irinotecan hydrochloride 3 H_2O is 350 mg/m^2.
- In patients with bilirubin levels 1.5 times to 3 times ULN, the recommended dose of irinotecan hydrochloride 3 H_2O is 200 mg/m^2.
- Patients with bilirubin levels above 3 times ULN must not be treated with irinotecan (see sections 4.3 and 4.4).

Combination therapy
No data are available for patients with impaired hepatic function treated with irinotecan in combination with other medicinal products.

Patients with impaired renal function

Irinotecan is not recommended for use in patients with impaired renal function, as no clinical studies have been performed in this patient population (see sections 4.4 and 5.2).

Elderly patients

No specific pharmacokinetic studies have been performed in elderly patients. However, the dosage should be chosen carefully in this patient population due to the greater incidence of impaired biological functions. This population requires more intense monitoring (see section 4.4).

Paediatric population

The safety and efficacy of irinotecan in children and adolescents have not yet been established. No data are available.

Method of administration

Precautions to be taken before handling or administering the medicinal product

Irinotecan is cytotoxic. For instructions on dilution of the medicinal product before administration and special precautions to be taken when handling and disposing of the medicinal product, see section 6.6.

4.3 Contraindications

- Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Breast-feeding (see section 4.4 and 4.6).

- Bilirubin levels > 3 times the upper limit of normal (ULN) (see section 4.4).
- Severe bone marrow dysfunction.
- WHO performance status > 2.
- Concomitant use of St. John's wort products (see section 4.5).
- Attenuated live vaccines (see section 4.5).

For additional contraindications of cetuximab or bevacizumab or capecitabine, please refer to the Summaries of Product Characteristics for these medicinal products.

4.4 Special warnings and precautions for use

The use of irinotecan must be restricted to facilities specialising in the administration of cytotoxic chemotherapy and must always be supervised by a physician qualified in the use of anticancer chemotherapy.

Given the nature and frequency of undesirable effects, irinotecan may be prescribed only after the expected benefit has been weighed against the possible therapeutic risks in the following cases:

- In patients with a risk factor, in particular in patients with WHO performance status = 2.
- In the few rare cases where it is unlikely that the patients will comply with the recommendations for treatment of undesirable effects (need for immediate and prolonged anti-diarrhoea treatment combined with a high fluid intake at the onset of delayed diarrhoea). Strict monitoring in hospital is recommended for such patients.

When irinotecan is used in monotherapy, it is usually prescribed using a three-week dosage regimen. However, a weekly dosage regimen may be considered in patients who require more intense monitoring or who are at particular risk of severe neutropenia (see section 5.1).

Delayed diarrhoea

Patients must be made aware of the risk of delayed diarrhoea, which may occur more than 24 hours after the administration of irinotecan and at any stage before the next treatment cycle. In monotherapy, the mean time until onset of the first liquid stool was day 5 after the infusion of irinotecan. Patients should promptly inform their physician of the occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who have had previous abdominal/pelvic radiotherapy, those with hyperleukocytosis before the start of therapy, those with performance status ≥ 2 and women. If the diarrhoea is not treated appropriately, it can be life-threatening, in particular if the patient experiences concomitant neutropenia.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of fluids containing electrolytes, and appropriate anti-diarrhoea therapy must be initiated immediately. Appropriate arrangements must be made to ensure that the physician who has administered irinotecan will also prescribe the anti-diarrhoea treatment. The patients must also receive the prescribed drugs after discharge from the hospital so that the diarrhoea can be treated as soon as it occurs. In addition, they must inform the treating physician or the institution where irinotecan was administered once/if diarrhoea occurs.

The anti-diarrhoea treatment currently recommended consists of high doses of loperamide (4 mg at the start, followed by 2 mg every 2 hours). This treatment should be continued for 12 hours after the last liquid stool and must not be modified. Due to the risk of paralytic ileus, loperamide may under no circumstances be administered for more than 48 consecutive hours at these doses, and the treatment must last at least 12 hours.

In addition to the anti-diarrhoea treatment, a broad-spectrum antibiotic should be administered as prophylaxis if the diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm^3).

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

- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous rehydration),
- Diarrhoea persisting beyond 48 hours after initiation of treatment with high doses of loperamide.

Loperamide must not be administered as prophylaxis, even in patients who have had delayed diarrhoea during previous treatment cycles of the medicinal product.

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

Haematology

In clinical studies, the frequency of grade 3 and 4 neutropenia as per the NCI-CTC standard was significantly higher in patients who had previously received pelvic/abdominal radiotherapy than in patients who had not received such radiotherapy. Patients with total bilirubin levels of 1.0 mg/dl or more before the start of treatment also were significantly likelier during the first cycle to experience grade 4 or 4 neutropenia than those with bilirubin levels below 1.0 mg/dl.

During treatment with irinotecan, weekly monitoring of complete blood counts is recommended. Patients must be informed about the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature > 38 °C and neutrophil count ≤ 1000 cells/mm^3) should be urgently treated in hospital with intravenous broad-spectrum antibiotics.

In patients experiencing severe haematological events, a dose reduction is recommended for subsequent administrations (see section 4.2).

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. In these patients, a complete blood count must be performed.

Impaired liver function

Liver function tests must be performed before the start of treatment and prior to each treatment cycle.

In patients with bilirubin values ranging from 1.5 to 3 times ULN, weekly complete blood count monitoring should be conducted due to the decreased clearance of irinotecan (see section 5.2) and thus increased risk of haematotoxicity in this population. For patients with bilirubin levels > 3 times ULN, see section 4.3.

Nausea and vomiting

Prophylactic treatment with an antiemetic is recommended before each administration of irinotecan. Nausea and vomiting occur frequently. Patients experiencing vomiting associated with delayed diarrhoea should be admitted for inpatient treatment as soon as possible.

Acute cholinergic syndrome

If acute cholinergic syndrome occurs (defined as early diarrhoea and certain other signs and symptoms such as sweating, abdominal cramps, miosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (see section 4.8).

These symptoms may be observed during or shortly after an irinotecan infusion. It is assumed that they are associated with the inhibitory effect of the parent substance irinotecan on cholinesterase, and they are expected to occur more frequently at higher irinotecan doses.

Caution should be exercised in patients with asthma. In patients who have experienced an acute and severe cholinergic syndrome, prophylactic use of atropine sulphate is recommended for subsequent irinotecan doses.

Respiratory diseases

During therapy with irinotecan, there have been uncommon cases of interstitial lung disease, manifesting as pulmonary infiltrates. Interstitial lung disease can be fatal. Risk factors possibly associated with the development of interstitial lung disease include the use of pneumotoxic medicinal products, radiotherapy and colony-stimulating factors.
Patients with risk factors should be closely monitored for respiratory symptoms before and during therapy with irinotecan.

Paravasation

Although irinotecan is not known to be a vesicant medicinal product, care should be taken to avoid paravasation, and the infusion site should be monitored for signs of inflammation. Should paravasation occur, flushing the site and application of ice is recommended.

Elderly patients

Due to a greater incidence of decreased biological functions in elderly patients, in particular of the hepatic function, the dose of irinotecan should be selected carefully in this population (see section 4.2).

Chronic inflammatory bowel disease and/or bowel obstruction

Patients must not be treated with irinotecan as long as bowel obstruction is present (see section 4.3).

Renal function

Elevated serum creatinine and blood urea nitrogen levels have been observed. There have been cases of acute renal failure. These events were generally attributed to complications of an infection or dehydration in connection with nausea, vomiting or diarrhoea. Rare cases of renal dysfunction due to tumour lysis syndrome have also been reported.

Radiotherapy

In patients who have previously undergone pelvic/abdominal radiotherapy, the risk of myelosuppression after administration of irinotecan is increased. When treating patients who have undergone extensive previous radiotherapy (e.g. radiation of > 25% of the bone marrow, and within 6 weeks of the start of treatment with irinotecan), care must be taken. A dose adjustment may be necessary in this population (see section 4.2).

Cardiac disorders

Myocardial ischaemic events have been observed following therapy with irinotecan predominately in patients with cardiac disorders, other known risk factors for cardiac disorders, or prior cytotoxic chemotherapy (see section 4.8).

Consequently, patients with known risk factors should be closely monitored, and actions should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Vascular disorders

In rare cases, irinotecan has been associated with thromboembolic events (pulmonary embolism, vein thrombosis and arterial thromboembolism) in patients with multiple risk factors in addition to the underlying neoplastic disorder.

Effects of immunosuppressants/increased susceptibility to infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicinal products including irinotecan may result in serious or fatal infections. Vaccination with a live vaccine is contraindicated during and 6 months after the cessation of the chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Patients with reduced UGT1A1 activity

Patients that are UGT1A1 poor metabolisers, such as patients with Gilbert's syndrome (e.g. homozygous for UGT1A1*28 or *6 variants) are at increased risk for severe neutropenia and diarrhoea following irinotecan treatment. This risk increases with the irinotecan dose level.

Although a precise dose reduction in starting dose has not been established, a reduced irinotecan starting dose should be considered for patients that are UGT1A1 poor metabolisers, especially patients who are administered doses > 180 mg/m^2 or frail patients. Consideration should be given to applicable clinical guidelines for dose recommendations in this patient population. Subsequent doses may be increased based on individual patient tolerance to treatment.

UGT1A1 genotyping can be used to identify patients at increased risk of severe neutropenia and diarrhoea, however the clinical utility of pre-treatment genotyping is uncertain, since UGT1A1 polymorphism does not account for all the toxicity seen from irinotecan therapy (see section 5.2).

Miscellaneous

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

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St. John's Wort, apalutamide) of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan and should be avoided (see section 4.5).

Contraception in women of childbearing potential/men:
Due to the potential for genotoxicity, female patients of reproductive potential are advised to use highlyeffective contraception during treatment and for 6 months after the last dose of irinotecan.

Due to the potential for genotoxicity, male patients with female partners of reproductive potentialare advised to use effective contraception during treatment and for 3 months after the last dose of irinotecan (seesection 4.6).

Breast-feeding
Due to the potential for adverse reactions in nursing infants, breast-feeding should be discontinued for the duration of Irinotecan therapy (see sections 4.3 and 4.6).

This medicinal product contains 0.1 mmol (or 2.4 mg) sodium per ml solution for injection. The various pack sizes of Irinotecan AqVida contain the following amounts of sodium:

2 ml-vial	The medicinal product in this pack size contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.
5 ml-vial	The medicinal product in this pack size contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.
15 ml-vial	The medicinal product in this pack size contains 36 mg sodium. This is equivalent to 1.8% of the WHO recommended maximum daily dietary intake of sodium for an adult (2 g).

25 ml-vial	The medicinal product in this pack size contains 60 mg sodium. This is equivalent to 3 % of the WHO recommended maximum daily dietary intake of sodium for an adult (2 g).

Irinotecan AqVida contains sorbitol. Patients with rare hereditary problems of fructose intolerance must not take this medicine unless absolutely necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration contraindicated (see section 4.3)

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

Attenuated live vaccines(e.g. yellow fever vaccine): risk of a generalised reaction to vaccines, possibly fatal. Concomitant useis contraindicated during treatment with irinotecan and for 6 months following discontinuation of chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Concomitant administration not recommended (see section 4.4)

Concurrent administration of irinotecan with strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan and should be avoided (see section 4.4):

Strong CYP3A4 and/or UGT1A1 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, or apalutamide):

Risk of decreased irinotecan, SN-38 and SN-38 glucuronide exposure and decreased pharmacodynamic effects. Various studies have shown that concomitant administration of CYP3A4 inducers as anticonvulsant drugs results in a reduced irinotecan, SN-38 and SN-38 glucuronide exposure and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs were reflected in a decrease in the AUC of SN-38 and SN-38G by 50% or more. Besides the induction of cytochrome P450 3A4 enzymes, increased glucuronidation and increased biliary excretion might also play a role in reducing exposure to irinotecan and its metabolites.

Additionally, for phenytoin: risk of exacerbation of convulsions resulting from the decrease of digestive phenytoin absorption caused by cytotoxic drugs.

Strong CYP3A4 inhibitors: (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, protease inhibitors, clarithromycin, erythromycin, telithromycin):
A study has shown that co-administration of ketoconazole resulted in a decrease in the AUC of APC by 87% and in an increase in the AUC of SN-38 by 109% versus irinotecan given alone.

UGT1A1 inhibitors: (e.g. atazanavir, ketoconazole, regorafenib)
Risk of increased systemic exposure of SN-38, the active metabolite of irinotecan. This must be taken into account if the combination cannot be avoided.

Other CYP3A4 inhibitors: (e.g. crizotinib, idelalisib)
Risk of increased toxicity of irinotecan as the metabolisation of irinotecan is decreased by crizotinib or idelalisib.

Take care with use

Vitamin K antagonists: Increased risk of haemorrhagic and thrombotic events in patients with tumour diseases. If vitamin K antagonists are indicated, more frequent monitoring of INR (International Normalised Ratio) is required.

To be taken into account in case of co-administration

Immunosuppressants (e.g. cyclosporine, tacrolimus): Excessive immunosuppression with the risk of lymphoproliferation.

Neuromuscular blocking agents: Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. As irinotecan displays anticholinesterase activity, medicines with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and antagonise the neuromuscular blockade of non-depolarising agents.

Other combinations

5-fluorouracil/folinic acid: Co-administration of 5-fluorouracil/folinic acid in a combination regimen does not alter the pharmacokinetics of irinotecan.

Bevacizumab: The results of a relevant interaction study did not reveal any significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN-38. An increase in toxicity due to the pharmacological properties cannot be ruled out, however.

Cetuximab: There is no evidence suggesting that the safety profile of irinotecan is affected by cetuximab, or vice versa.

Antineoplastic agents (including flucytosine as a prodrug for 5-fluorouracil):
Adverse effects of irinotecan, such as myelosuppression, may be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

4.6 Fertility, pregnancy and lactation

Contraception

Due to the potential for genotoxicity, female patients of reproductive potential are advised to use highlyeffective contraception during treatment and for 6 months after the last dose of irinotecan (see section4.4).

Due to the potential for genotoxicity, male patients with female partners of reproductive potential are advised to use effective contraception during treatment and for 3 months after the last dose of irinotecan (seesection 4.4).

Pregnancy

There are limited datafrom the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic and teratogenic in animals (see section 5.3). Therefore, based on results from animal studies and the mechanism of action of irinotecan, irinotecan must not be used during pregnancy unless absolutely necessary.
Women of childbearing potential should not be started on irinotecan until pregnancy is excluded.Pregnancy should be avoided if either partner is receiving irinotecan.

Breast-feeding

Theavailable data are limited but suggested that irinotecan and its metabolite are excreted in human milk. Consequently, breast-feeding must be discontinued during treatment with irinotecan due to the potential for undesirable effects in breast-feeding infants (see sections 4.3 und 4.4).

Fertility

No information for humans regarding the effect of irinotecan on fertility is available. In animals, undesirable effects of irinotecan on the fertility of offspring have been documented (see section 5.3).

Prior to starting touse Irinotecan patients should be advised on the preservation of gametes.

4.7 Effects on ability to drive and use machines

Irinotecan has moderate influence on the ability to drive and use machines. Patients should be warned about the possible occurrence of dizziness or visual disturbances, which may occur within 24 hours following the administration of irinotecan, and advised that they must not drive or use machines if these symptoms occur.

4.8 Undesirable effects

Clinical studies

A comprehensive collection of undesirable effects was conducted in studies in patients with metastatic colorectal cancer; the frequencies are stated below. In other indications, the adverse reactions are expected to be similar like for colorectal cancer.

The most common (≥ 1/10) dose-limiting undesirable effects of irinotecan include delayed diarrhoea (more than 24 hours after administration) and blood disorders, including neutropenia, anaemia, and thrombocytopenia.

Neutropenia is a dose-limiting toxic effect. Neutropenia was reversible and not cumulative; regardless of use as monotherapy or combination therapy, the lowest neutrophil counts were, as median, seen on day 8.

A transient, severe acute cholinergic syndrome was observed very commonly. The main symptoms occurring during or within the first 24 hours after the infusion with irinotecan were described as early diarrhoea and various other symptoms such as abdominal pain, sweating, miosis and increased salivation. These symptoms resolved after administration of atropine (see section 4.4).

Monotherapy and post-marketing surveillance

The following undesirable effects, which are possibly or likely due to the administration of irinotecan were collected in clinical trials and/or post-marketing surveillance in 765 patients receiving monotherapy at the recommended dose of 350 mg/m^2. The undesirable effects are indicated in decreasing degree of severity within each frequency group. The frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10 000, < 1/1000), very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 1

Undesirable effects reported on monotherapy with irinotecan hydrochloride 3 H_2O (dose regimen 350 mg/m^2 every 3 weeks)		
MedDRA System Organ Class	**Frequency**	**Preferred term**
Infections and infestations	Common	Infection
	Not known	Pseudomembranous colitis, one case of which has been documented bacteriologically (*Clostridium difficile*), sepsis, fungal infections[a], viral infections[b]
Blood and lymphatic system disorders	Very common	Neutropenia, anaemia
	Common	Thrombocytopenia, febrile neutropenia
	Not known	Peripheral thrombocytopenia with thrombocyte antibodies

Undesirable effects reported on monotherapy with irinotecan hydrochloride 3 H_2O (dose regimen 350 mg/m^2 every 3 weeks)		
MedDRA System Organ Class	**Frequency**	**Preferred term**
Immune system disorders	Not known	Hypersensitivity reactions, anaphylactic reactions
Metabolism and nutrition disorders	Very common	Decreased appetite
	Not known	Dehydration (due to diarrhoea and vomiting), hypovolaemia, hypomagnesiaemia, tumour lysis syndrome, hypokalaemia, hyponatraemia
Psychiatric disorders	Not known	Confusion
Nervous system disorders	Very common	Cholinergic syndrome
	Not known	Temporary speech disorders; in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after the irinotecan infusion; paraesthesia, headache, syncope
Cardiac disorders	Not known	Hypertension (during or after the infusion), cardiovascular failure*, cardiovascular disorders (angina pectoris, cardiac arrest, myocardial infarction, myocardial ischemia), bradycardia
Vascular disorders	Not known	Hypotension, flush, thromboembolic events (arterial thrombosis, cerebral infarction, cerebrovascular event, deep thrombophlebitis, embolism of the leg, pulmonary embolism, thrombophlebitis, thrombosis and sudden death), peripheral vascular disorder
Respiratory, thoracic and mediastinal disorders	Not known	Interstitial lung disease manifesting as pulmonary infiltrates, dyspnoea, hiccups
Gastrointestinal disorders	Very common	Diarrhoea, vomiting, nausea, abdominal pain
	Common	Constipation
	Not known	Bowel obstruction, ileus, megacolon, gastrointestinal haemorrhages, colitis including typhlitis, ischaemic and ulcerative colitis, gastrointestinal bleeding, symptomatic or asymptomatic increased pancreatic enzymes, intestinal perforation, fungi in the gastrointestinal tract
Hepatobiliary disorders	Common	Increased serum creatinine, transaminases increased (AST and ALT), increased bilirubin, alkaline phosphatase increased
	Not known	Increased GTP levels, hepatic steatosis, steatohepatitis, amylase increased, elevated lipase
Skin and subcutaneous tissue disorders	Very common	Alopecia (reversible)
	Not known	Skin reactions, skin rash
Musculoskeletal and connective tissue disorders	Not known	Muscle contractions or cramps
Renal and urinary disorders	Not known	Renal impairment and acute kidney injury, renal insufficiency, urinary tract infections
Reproductive system and breast disorders	Not known	Chest pain
General disorders and administration site conditions	Very common	Mucosal inflammation, pyrexia, asthenia
	Not known	Infusion site reactions, pain, abnormal gait, paravasation

[a]e.g. *Pneumocystis jirovecii* pneumonia, bronchopulmonary aspergillosis, systemic candida
[b]e.g. Herpes zoster, influenza, reactivation of hepatitis B and colitis caused by cytomegalovirus.

*Uncommon 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 had sepsis.

Description of selected undesirable effects (monotherapy)

Severe diarrhoea was observed in 20% of the patients who followed the recommendations for controlling diarrhoea. Severe diarrhoea was observed in 14% of the evaluable cycles. The median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.

Approximately 10% of the patients treated with an antiemetic drug experienced severe **nausea and vomiting**.

Constipation was observed in less than 10% of patients.

Neutropenia was observed in 78.7% of patients and was severe in 22.6% (neutrophil count < 500 cells/mm^3). Of the evaluable treatment cycles, 18% had a neutrophil count below 1000 cells/mm^3, including 7.6% with 500 cells/mm^3. Total recovery was usually reached by day 22.

Febrile neutropenia was observed in 6.2% of patients and 1.7% of cycles. **Infections** occurred in approximately 10.3% of patients (2.5% of cycles), and were associated with severe neutropenia in approximately 5.3% of patients (1.1% of cycles); two cases were fatal.

Anaemia was reported in approximately 58.7% of patients (8% with haemoglobin levels < 8 g/dl and 0.9% with haemoglobin levels < 6.5 g/dl).

Thrombocytopenia (< 100 000 cells/mm^3) was reported in 7.4% of patients and 1.8% of cycles, with thrombocyte counts of ≤ 50 000 cells/mm^3 observed in 0.9% of patients and 0.2% of cycles. Almost all patients had recovered by the 22nd day.

Acute cholinergic syndrome
Temporary, severe acute cholinergic syndrome was observed in 9% of patients receiving monotherapy.

Asthenia was serious in less than 10% of patients receiving monotherapy. A causal relationship with irinotecan could not be unambiguously demonstrated.

Pyrexia without infection or concomitant severe neutropenia occurred in 12% of patients receiving monotherapy.

Investigations
On monotherapy, temporary, mild to moderate increases in serum levels of transaminases were observed in 9.2%, of alkaline phosphatase in 8.1% and of bilirubin in 1.8% of patients without progressive liver metastases.
A temporary, mild to moderate increase in serum creatinine levels was observed in 7.3% of patients.

Combination therapy

The undesirable effects listed in this section refer to irinotecan.
There is no evidence suggesting that the safety profile of irinotecan is affected by cetuximab, or vice versa. The undesirable effects additionally observed in combination with cetuximab were in line with the effects expected for cetuximab (e.g. 88% acneiform dermatitis). For the undesirable effects of the combination of irinotecan and cetuximab, please also refer to the Summary of Product Characteristics of cetuximab.

In patients treated with irinotecan/capecitabine combination therapy, the following undesirable effects have been observed additionally or more frequently than in patients on capecitabine monotherapy: *Very common, undesirable effects of all severity grades*: thrombosis/embolism; *Common, undesirable effects of all severity grades*: hypersensitivity reaction, myocardial ischaemia/myocardial infarction;

Common, severity grade 3 and 4 undesirable effects: febrile neutropenia. For the full list of undesirable effects of capecitabine, please refer to the Summary of Product Characteristics of capecitabine.

In patients treated with irinotecan/bevacizumab/capecitabine combination therapy, the following severity grade 3 and 4 undesirable effects have been observed additionally or more frequently than in patients on capecitabine monotherapy: *Common, undesirable effects of severity grades 3 and 4:*neutropenia, thrombosis/embolism, hypertension and cardiac ischaemia/heart attack. For the full list of undesirable effects of capecitabine and bevacizumab, please refer to the Summaries of Product Characteristics of capecitabine and bevacizumab.

Grade 3 hypertension was the most important significant risk related to the combination of bevacizumab and irinotecan/5-FU/FA as bolus.
In addition, there was a small increase in the chemotherapy-related undesirable effects diarrhoea and leukopenia of severity grades 3 to 4 on this treatment regimen as compared to patients receiving irinotecan/5-FU/FA as bolus alone. For the undesirable effects in combination with bevacizumab, please refer to the Summary of Product Characteristics for bevacizumab.

Irinotecan in combination with 5-FU and FA has been investigated in patients with metastatic colorectal cancer. Data about undesirable effects from clinical studies show very common, possibly or likely treatment-related undesirable effects of severity grades 3 or 4 as per NCl in the MedDRA SOCs "Blood and lymphatic system disorders", "Gastrointestinal disorders" and "Skin and subcutaneous tissue disorders".

The following undesirable effects possibly or likely due to the administration of irinotecan were reported in 145 patients who had been treated with the recommended dose of 180 mg/m^2 irinotecan hydrochloride 3 H_2O in combination with 5-FU/FA every two weeks.

Table 2

Undesirable effects reported for irinotecan hydrochloride 3 H_2O in a combination therapy (dose regimen 180 mg/m^2 every 2 weeks)		
MedDRA System Organ Class	**Frequency**	**Preferred term**
Infections and infestations	Common	Infection
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, anaemia
	Common	Febrile neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Cholinergic syndrome
Gastrointestinal disorders	Very common	Diarrhoea, vomiting, nausea
	Common	Abdominal pain, constipation
Hepatobiliary disorders	Very common	Transaminases increased (AST and ALT), increased bilirubin, alkaline phosphatase increased
Skin and subcutaneous tissue disorders	Very common	Alopecia (reversible)
General disorders and administration site conditions	Very common	Mucosal inflammation, asthenia
	Common	Pyrexia

Description of selected undesirable effects (combination therapy)

Severe diarrhoea was observed in 13.1% of the patients who followed the recommendations for controlling diarrhoea. Severe diarrhoea was observed in 3.9% of the evaluable cycles.

Nausea and vomiting in serious form were observed less frequently (2.1% and 2.8% of patients, respectively).

Constipation in connection with irinotecan and/or loperamide was observed in 3.4% of patients.

Neutropenia was observed in 82.5% of patients and was severe in 9.8% (neutrophil count < 500 cells/mm^3). Of the evaluable treatment cycles, 67.3% had a neutrophil count below 1000 cells/mm^3 including 2.7% with <500 cells/mm^3. Total recovery was usually reached within 7-8 days.

Febrile neutropenia was observed in 3.4% of patients and 0.9% of cycles.**Infections** occurred in approximately 2% of patients (0.5% of cycles), and were associated with severe neutropenia in approximately 2.1% of patients (0.5% of cycles); one case was fatal.

Anaemia was reported in approximately 97.2% of patients (2.1% with haemoglobin levels < 8 g/dl).

Thrombocytopenia (< 100 000 cells/mm^3) was reported in 32.6% of patients and 21.8% of cycles; there was no case of severe thrombocytopenia (≤ 50 000 cells/mm^3).

Acute cholinergic syndrome
Temporary, severe acute cholinergic syndrome was observed in 1.4% of patients receiving combination therapy.

Asthenia was serious in 6.2% of patients receiving combination therapy. A causal relationship with irinotecan could not be unambiguously demonstrated.

Pyrexia without an infection or concomitant severe neutropenia occurred in 6.2% of patients receiving combination therapy.

Investigations
Transient (grade 1 and grade 2) serum level increases of either SGOT, SGPT, alkaline phosphatase or bilirubin have been observed in 15%, 11%, 11% and 10%, respectively, of patients without progressive liver metastases. Transient increase to grade 3 was observed in 0%, 0%, 0% and 1%, respectively, of those patients. Grade 4 has not been observed.
In rare cases, a transient increase in amylase and/or lipase has been reported.
Furthermore, rare cases of hypokalaemia and hyponatraemia have been reported, mostly in connection with the onset of diarrhoea and vomiting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national competent authority.

4.9 Overdose

Symptoms

There have been reports of overdoses with doses up to approximately twice the recommended therapeutic dose, which may be fatal. The undesirable effects reported were mostly severe neutropenia and severe diarrhoea.

Treatment

There is no known antidote for irinotecan. Best supportive care is required to prevent dehydration due to diarrhoea and to treat any infectious complications.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01CE02.

Mechanism of action

Experimental data

Irinotecan is a semisynthetic derivative of camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. In most tissues, irinotecan is metabolised by carboxylesterases to SN-38, which has been found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several human and murine tumour cell lines. Inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand breaks in the DNA which block the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic effect was found to be time-dependent and S-phase specific.
In vitro, irinotecan and SN-38 are not significantly recognised by P-glycoprotein (MDR), and irinotecan displayed cytotoxic activity against celllines resistant to doxorubicin and vinblastine.

In addition, irinotecan *in vivo* shows broad antitumour activity 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 tumours expressing P-glycoprotein (MDR) (P388 leukaemia resistant to doxorubicin and vincristine).

In addition to the antitumour activity of irinotecan, the most important pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

Clinical data

Combination therapy: First-line therapy of metastatic colorectal cancer

Combination therapy with folinic acid and 5-fluorouracil
A phase III study was conducted on 385 patients with metastatic colorectal cancer receiving first-line therapy, administered either every 2 weeks (see section 4.2) or every week. In the fortnightly therapy regimen, the administration of 180 mg/m^2 irinotecan hydrochloride 3 H_2O once every 2 weeks on Day 1 was followed by infusion of folinic acid (200 mg/m^2 as a 2-hour intravenous infusion) and of 5-fluorouracil (400 mg/m^2 as an intravenous bolus injection, followed by 600 mg/m^2 as a 22-hour intravenous infusion). On Day 2, folinic acid and 5-fluorouracil were administered using the same dosage and therapeutic regimen. In the weekly regimen, the administration of 80 mg/m^2 irinotecan hydrochloride 3 H_2O was followed by infusion of folinic acid (500 mg/m^2 as a 2-hour intravenous infusion) and then of 5-FU (2300 mg/m^2 as a 24-hour intravenous infusion) over 6 weeks.

In the combination therapy with the two regimens described above, the efficacy of irinotecan was analysed for 198 patients:

Table 3

	Combined regimen (n = 198)		Weekly treatment (n = 50)		Treatment every 2 weeks (n = 148)	
	Irinotecan-HCl + 5FU/FA	5-FU/ FA	Irinotecan-HCl+ 5FU /FA	5-FU/ FA	Irinotecan-HCl+ 5-FU/FA	5-FU/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 effect [months]	9.3	8.8	8.9	6.7	9.3	9.5
p value	NS		p = 0.043		NS	
Median duration of effect 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	

5-FU: 5-fluorouracil
FA: folinic acid
NS: not significant
*: according to per-protocol population analysis

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

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

Quality of life was assessed in this phase III study based on the EORTC QLQ-C30 questionnaire. Time to definitive deterioration was constantly later in the groups treated with irinotecan. Global health status/quality of life was slightly better in the irinotecan combination group, although not significantly, showing that efficacy of irinotecan in combination treatment can be achieved without affecting the quality of life.

Combination therapy with bevacizumab
In a randomised, double-blind, active-controlled clinical phase III study, bevacizumab in combination with irinotecan/5-FU/FA was investigated as first-line therapy in patients with metastatic colorectal cancer (AVF2107g study). Administration of bevacizumab in addition to the combination irinotecan/5-FU/FA resulted in statistically significantly prolonged overall survival. The clinical benefit of the combination therapy measured based on the overall survival was present in all previously defined subgroups (patients stratified according to age, gender, performance status, location of primary tumour, number of affected organs and duration of metastatic disease). In this context, please refer to the Summary of Product Characteristics for bevacizumab. The efficacy results of the AVF2107g study are summarised in the table below.

Table 4

	AVF2107g	
	Arm 1 Irinotecan/5-FU/FA Placebo	**Arm 2 Irinotecan/5-FU/FA Bevacizumab[a]**
Sample size	411	402
Overall survival		
Median survival [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 duration [months]	6.2	10.6
Hazard ratio [b]		0.54
p value		< 0.0001
Overall response rate		
Rate [%]	34.8	44.8
95% Confidence interval	30.2–39.6	39.9–49.8
p value		0.0036
Duration of effect		
Median duration [months]	7.1	10.4
25^{th}–75^{th} percentiles [months]	4.7–11.8	6.7–15.0

[a] 5 mg/kg every 2 weeks.
[b] In relation to the control arm

Combination therapy with cetuximab
EMR 62 202-013: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for their metastatic disease compared the combination of cetuximab and irinotecan plus infusions of 5-Fluorouracil/Folinic Acid (5-FU/FA) (599 patients) to the same chemotherapy without cetuximab (599 patients). The proportion of patients with KRAS wild-type tumours within the population evaluable for KRAS status was 64%.

The efficacy data from this study are summarised in the table below.

Table 5

	Total population		**KRAS wild-type population**	
Variable/statistical	**Cetuximab + FOLFIRI (n = 599)**	**FOLFIRI (n = 599)**	**Cetuximab + FOLFIRI (n = 172)**	**FOLFIRI (n = 176)**
ORR				
% (95% CI)	46.9 (42.9; 51.0)	38.7 (34.8; 42.8)	59.3 (51.6; 66.7)	43.2 (35.8; 50.9)
p value	0.0038		0.0025	
PFS				
Hazard ratio (95% CI)	0.85 (0.726; 0.998)		0.68 (0.501; 0.934)	
p value	0.0479		0.0167	

CI: confidence interval; FOLFIRI: irinotecan + intravenous 5-FU/FA; ORR: objective response rate (patients with complete response or partial response); PFS: progression-free survival

Combination therapy with capecitabine
The results of a randomised, controlled phase III study (CAIRO) support the use of capecitabine at a starting dose of 1000 mg/m^2 (for 2 weeks every 3 weeks) in combination with irinotecan hydrochloride 3 H_2O for the first-line treatment of patients with metastatic colorectal cancer. 820 patients were randomised to receive either sequential treatment (n = 410) or combination treatment (n = 410). Sequential treatment consisted of a first-line treatment with capecitabine

(1250 mg/m^2 twice daily for 14 days), second-line treatment with irinotecan hydrochloride 3 H_2O (350 mg/m^2 on Day 1), and third-line treatment with a combination of capecitabine (1000 mg/m^2 twice daily for 14 days) and oxaliplatin (130 mg/m^2 on Day 1). Combination treatment consisted of first-line treatment with capecitabine (1000 mg/m^2 twice daily for 14 days) combined with irinotecan hydrochloride 3 H_2O (250 mg /m^2 on Day 1) (XELIRI) and second-line treatment with capecitabine (1000 mg/m^2 twice daily for 14 days) plus oxaliplatin (130 mg/m^2 on Day 1). All treatment cycles were administered in 3-week intervals. In first-line treatment, the median progression-free survival in the intent-to-treat population was 5.8 months (95% CI, 5.1-6.2 months) for capecitabine monotherapy and 7.8 months (95% CI, 7.0-8.3 months) for XELIRI (p = 0.0002).

The results of an interim analysis of a multicentre, randomised, controlled phase II study (AIO KRK 0604) support the use of capecitabine at a starting dose of 800 mg/m^2 (for 2 weeks every 3 weeks) in combination with irinotecan hydrochloride and bevacizumab as first-line treatment of patients with metastatic colorectal cancer. 115 patients were randomised to treatment with capecitabine combined with irinotecan (XELIRI) and bevacizumab: capecitabine (800 mg/m^2 twice daily for two weeks, followed by a 7-day rest period), 200 mg/m^2 irinotecan hydrochloride 3 H_2O administered as a 30-minute infusion on Day 1 every 3 weeks and 7.5 mg/kg bevacizumab as a 30- to 90-minute infusion on Day 1 every 3 weeks. A total of 118 patients were randomised to treatment with capecitabine combined with oxaliplatin plus bevacizumab: capecitabine (1000 mg/m^2 twice daily for two weeks, followed by a 7-day rest period), 130 mg/m^2 oxaliplatin administered as a 2-hour infusion on Day 1 every 3 weeks and 7.5 mg/kg bevacizumab as a 30- to 90-minute infusion on Day 1 every 3 weeks. In the intent-to-treat population, progression-free survival after 6 months was 80% (XELIRI plus bevacizumab) versus 74% (XELOX plus bevacizumab). Overall response rate (patients with complete response or partial response) was 45% (XELOX plus bevacizumab) versus 47% (XELIRI plus bevacizumab).

Monotherapy: Second-line therapy of metastatic colorectal cancer

More than 980 patients with metastatic colorectal cancer who had not responded to previous 5-FU treatment were enrolled in clinical phase II/III studies with the 3-weekly dosage regimen. The efficacy of irinotecan hydrochloride was evaluated in 765 patients with disease progression during the 5-FU treatment at baseline.

Table 6

	Phase III					
	Irinotecan vs. supportivecare			Irinotecan vs. 5-FU		
	Irinotecan HCl (n = 183)	Supportive care (n = 90)	p value	Irinotecan HCl (n = 127)	5-FU (n = 129)	p value
Progression-free survival rate after 6 months [%]	N/A	N/A		33.5*	26.7	0.03
Survival rate after 12 months [%]	36.2*	13.8	0.0001	44.8*	32.4	0.0351
Median survival [months]	9.2*	6.5	0.0001	10.8*	8.5	0.0351

N/A: not applicable
*: statistically significant difference

In phase II studies conducted in 455 patients with the 3-weekly dosing regimen, the disease-free survival rate after 6 months was 30%, and the median survival time was 9 months. The median time to progression was 18 weeks.

Additionally, non-comparative phase II studies were conducted on 304 patients with weekly administration of a dose of 125 mg/m^2 BSA as an intravenous infusion over a period of 90 minutes during 4 consecutive weeks, followed by a rest period of 2 weeks. In these studies, the median time to the onset of progression was 17 weeks, and the median survival time was 10 months. A similar safety profile to the 3-weekly dosing schedule was observed for the weekly dosing regimen in 193 patients with a starting dose of 125 mg/m^2 BSA. The median time to onset of liquid stools was Day 11.

Combination therapy with cetuximab in patients who did not respond to previous chemotherapy containing irinotecan

The efficacy of a combination of cetuximab and irinotecan was investigated in two clinical studies. A total of 356 patients with EGFR-expressing metastatic colorectal cancer in whom a cytotoxic therapy including irinotecan had recently failed and had a minimum Karnofsky performance status of 60% (the majority had a Karnofsky performance status of ≥ 80%) were treated with 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 following:

Table 7

Study	n	ORR		DCR		PFS [months]		OS [months]	
		n (%)	95% CI	n (%)	95% CI	Median	95% CI	Median	95% CI
Cetuximab and 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 or partial response to the treatment or whose condition remained stable for at least 6 weeks); ORR: objective response rate: patients with complete or partial response to the treatment; OS: overall survival; PFS: progression-free survival

The efficacy of the combination therapy with cetuximab and irinotecan was shown to be higher than 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 rate were demonstrated (hazard ratio 0.91, p = 0.48).

5.2 Pharmacokinetic properties

Absorption

At the end of the infusion of the recommended dose of 350 mg/m^2, the mean maximum plasma concentration of irinotecan hydrochloride 3 H_2O and SN-38 was 7.7 µg/ml and 56 ng/ml, and the mean AUC (area under curve) values were 34 µg h/ml and 451 ng h/ml, respectively. For SN-38, great interindividual variability in pharmacokinetic parameters can generally be observed.

Distribution

The phase I study in 60 patients on a dosage regimen with a 30-minute intravenous infusion of 100 to 750 mg/m^2 every 3 weeks showed a volume of distribution at steadystate (Vdss) of 157 l/m^2.

In vitro, plasma protein binding of irinotecan and SN-38 was approximately 65% and95%, respectively.

Biotransformation

Mass balance and metabolic studies conducted with ^{14}C-labelled product showed that more than 50% of the dose of irinotecan administered intravenously is excreted as unchanged drug (33% is eliminated in faeces, mainly by bile, and 22% with urine).

Two metabolic pathways are responsible for metabolising at least 12% of a dose each:

- Hydrolysis mediated by carboxylesterases to the active metabolite SN-38: SN-38 is eliminated primarily by glucuronidation and furthermore excreted by renal and biliary elimination (less than 0.5% of the irinotecan dose). It is likely that the SN-38glucuronide is subsequently hydrolysed in the intestines.
- Oxidation promoted by the CYP3A enzymes, resulting in the opening of the outer piperidine ring and the formation of the aminopentanoic acid derivative (APC) and a primary amine derivative (NPC) (see section 4.5).

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

Elimination

In a phase I study on 60 patients on a dosage regimen with an intravenous infusion of 30 minutes with 100 to 750 mg/m^2 every three weeks, irinotecan hydrochloride displayed a biphasic or triphasic elimination profile. Mean plasma clearance was 15 l/h/m^2. The mean plasma half-life was 12 minutes in the first phase of the triphasic model, 2.5 hours in the second phase, and 14.2 hours in the terminal phase. SN-38 displayed a biphasic elimination profile with a mean half-life of 13.8 hours in the terminal phase.

Irinotecan clearance decreases by approximately 40% in patients with bilirubinaemia between 1.5 and 3 times of the upper normal value. In these patients, a dose of 200 mg/m^2 of irinotecan hydrochloride 3 H_2O results in a drug exposure in plasma comparable to that observed at a dose of 350 mg/m^2 in cancer patients with normal liver parameters.

Linearity/non-linearity

A population pharmacokinetic analysis of irinotecan was conducted in 148 patients with metastatic colorectal cancer, treated with various regimens and at different doses in phase II trials. The pharmacokinetic parameters calculated using a 3-compartment model were similar to those observed in phase I studies. All studies have shown that the irinotecan (CPT-11) and SN-38 exposure increases proportionally with the CPT-11 dose administered; its pharmacokinetics is independent of the number of previous cycles and of the administration regimen.

Pharmacokinetic/pharmacodynamic relationship(s)

The intensity of the major toxicities arising with irinotecan (e.g. leukopenia/neutropenia and diarrhoea) is related to the exposure (AUC) to the parent drug and the metabolite SN-38. In monotherapy, significant correlations were observed between the haematologic toxicity (decrease in leukocyte and neutrophil count at nadir) or the intensity of diarrhoea and the AUC values, both of irinotecan and of the metabolite SN-38.

Patients with Reduced UGT1A1 activity:
Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is involved in the metabolic deactivation of SN-38, the active metabolite of irinotecan to inactive SN-38 glucuronide (SN-38G). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. The most well-characterized UGT1A1 genetic variants are UGT1A1*28 and UGT1A1*6. These variants and other congenital deficiencies in UGT1A1 expression (such as Gilbert's syndrome and Crigler-Najjar) are associated with reduced activity of this enzyme.

Patients that are UGT1A1 poor metabolisers (e.g. homozygous for UGT1A1*28 or *6 variants) are at increased risk of severe adverse reactions such as neutropenia and diarrhoea following administration of irinotecan, as a consequence of SN-38 accumulation. According to data from several meta-analyses, the risk is higher for patients receiving irinotecan doses > 180 mg/m^2 (see section 4.4).

In order to identify patients at increased risk of experiencing severe neutropenia and diarrhoea, UGT1A1 genotyping can be used. Homozygous UGT1A1*28 occurs with a frequency of 8–20% in the European, African, Near Eastern and Latino population. The *6 variant is nearly absent in these populations. In the East Asian population the frequency of *28/*28 is about 1–4%, 3–8% for*6/*28 and 2–6% for *6/*6. In the Central and South Asian population the frequency of *28/*28 is around 17%, 4% for *6/*28 and 0.2% for *6/*6.

5.3 Preclinical safety data

Irinotecan and SN-38 were shown to be mutagenic *in vitro* in the chromosomal aberration assay in CHO cells as well as *in vivo* in the micronucleus test in mice.

However, they were shown not to have any mutagenic potential in the Ames test.

In rats treated once a week for 13 weeks with a maximum dose of 150 mg/m^2 (i.e. less than half the recommended human dose), there were no treatment-related tumours reported within a period of 91 weeks after cessation of therapy.

Single-dose and repeat-dose toxicity studies have been performed in mice, rats and dogs. The most important toxic effects affected the lymphatic and haematopoietic systems. In dogs, delayed diarrhoea associated with atrophy and focal necrosis of the intestinal mucosa was reported. Furthermore, alopecia was also observed in dogs.

The severity of these effects was dose-related, and they were reversible.

Reproduction

In rats and rabbits, irinotecan was teratogenic at doses below the therapeutic human dose. In rats, the offspring of treated animals with external abnormalities displayed decreased fertility. This was not observed in morphologically normal offspring. In pregnant rats, decreased placental weight was observed, and the offspring displayed reduced foetal survival and an increase in abnormal behaviours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (Ph. Eur.)
Lactic acid
Sodium hydroxide
Water for injection

6.2 Incompatibilities

Irinotecan HCl AqVida is compatible with 0.9% sodium chloride solution and 5% glucose solution. Do not combine with other medicinal products.

6.3 Shelf life

Unopened vial: 3 years

After dilution: The chemical and physical stability of the ready-to-use solution for infusion after reconstitution with 0.9% sodium chloride solution or 5% glucose solution was demonstrated for 12 hours at 15 to 25°C and for 48 hours when protected from light at 2 to 8°C.

From a microbiological standpoint, the ready-to-use solution for infusion should be used immediately. If not used immediately, the shelf life and storage conditions until use are the responsibility of the user and should not exceed 24 hours at 2 to 8°C, unless the dilution was carried out under controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
Do not freeze.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 ml, 5 ml, 20 ml and 25 ml brown glass vials contain 2 ml, 5 ml, 15 ml and 25 ml concentrate for solution for infusion. The vials are sealed with a halobutyl rubber stopper with an aluminium cap.
Single pack and multiple pack of 5 or 10 packs each containing 1 vial with 2 ml of solution.
Single pack and multiple pack of 5 or 10 packs each containing 1 vial with 5 ml of solution.
Single pack and multiple pack of 5 or 10 packs each containing 1 vial with 15 ml of solution.
Single pack and multiple pack of 5 or 10 packs each containing 1 vial with 25 ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Irinotecan HCl AqVida is a cytotoxic product. Please comply with your local rules on the safe handling and safe disposal of cytostatics.

Safe handling

Like all antineoplastic agents, irinotecan must be reconstituted and handled with care. Goggles, a mask and gloves must be worn. If irinotecan solution or the solution for infusion comes into contact with skin, immediately wash thoroughly with soap and water. If irinotecan solution or the solution for infusion comes into contact with mucous membranes, immediately wash thoroughly with water.

Preparation of the solution for infusion

Irinotecan HCl AqVida solutions should be prepared under controlled and validated aseptic conditions.

If a deposit can be seen in the vial or after dilution, the medicinal product should be disposed of in accordance with the usual standards for cytostatic active substances.
To prepare the solution, remove the required amount of Irinotecan HCl AqVida with a calibrated syringe under aseptic conditions from the vial and inject it into a 250 ml infusion bag/infusion bottle containing either 0.9% sodium chloride solution or 5% glucose solution. Then mix thoroughly by tilting manually.

Disposal

Only for single use. All materials used for preparation and administration or otherwise coming into contact with Irinotecan HCl AqVida in any way must be disposed of according to national guidelines for handling cytotoxic agents.

7. MARKETING AUTHORISATION HOLDER

AqVida GmbH
Kaiser-Wilhelm-Str. 89
20355 Hamburg
Germany

8. MARKETING AUTHORISATION NUMBER(S)

07594/08749/NMR/2020

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

04-08-2022

10. DATE OF REVISION OF THE TEXT

01/2023

11. PRESCRIPTION STATUS

Prescription-only medicinal product