Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Camrata 20 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 20 mg irinotecan hydrochloride trihydrate (equivalent to 17.33 mg/ml irinotecan).

Each 2ml vial contains 40 mg of irinotecan hydrochloride trihydrate.

Each 5ml vial contains 100 mg of irinotecan hydrochloride trihydrate.

Excipients:

Also contains sorbitol (E420) 45 mg/ml and sodium (see Section 4.4)

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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

Camrata in combination with cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer, who had not received prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy (see Section 5.1).

Camrata in combination with 5-FU, FA and bevacizumab is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

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

4.2 Posology and method of administration

For use in adults only.

Camrata should be infused into a peripheral or central vein.

See Section 6.6 for instructions on the preparation and use of the intravenous administration solution.

Recommended dosage:

In monotherapy (for previously treated patient):

The recommended dosage of Camrata is 350 mg/m^2 administered as an intravenous infusion over a 30 to 90 minute period every three weeks (see Section 4.4).

In combination therapy (for previously untreated patient):

Safety and efficacy of irinotecan in combination with 5-FU and FA have been assessed with the following schedule (see Section 5.1):

- Irinotecan plus 5-FU/FA in every 2 weeks schedule

The recommended dose of Camrata is 180 mg/m^2 administered once every 2 weeks as an intravenous infusion over a 30 to 90 minute period, followed by infusion with FA and 5-FU.

For the posology and method of administration of concomitant cetuximab, refer to the summary of product characteristics of this medicinal product. Normally, the same dose of irinotecan is used as administered in the last cycles of the prior irinotecan-containing regimen. Camrata 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 of product characteristics.

For the posology and method of administration of capecitabine combination, see Section 5.1 and refer to the appropriate sections in the capecitabine summary of product characteristics

Dosage adjustments:

Camrata 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 Camrata, and 5-FU 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 Camrata and/or 5-FU when applicable:

- haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3 - 4 and fever grade 2 - 4), thrombocytopenia and leucopenia (grade 4)),
- non-haematological toxicity (grade 3 - 4).

Recommendations for dose modification of cetuximab when administered in combination with Camrata must be followed according to the summary of product characteristics for this medicinal product.

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

In combination with capecitabine for patients 65 years of age or more, a reduction of the starting dose of capecitabine to 800 mg/m^2 twice daily is recommended according to the summary of product characteristics for capecitabine. Refer also to the recommendations for dose modifications in combination regimen given in the summary of product characteristics for capecitabine.

Treatment duration:

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

Special populations:

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 Camrata. In these patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased (see Section 5.1) and therefore the risk of haematoxicity is increased. Thus, weekly monitoring of complete blood counts should be conducted in this patient population.

- Patients with bilirubin up to 1.5 times the ULN, the recommended dosage of Camrata is 350 mg/m^2,
- Patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Camrata is 200 mg/m^2,
- Patients with bilirubin above 3 times the ULN should not be treated with Camrata (see Sections 4.3 and 4.4).

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

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 Sections 4.4 and 5.1).

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).

4.3 Contraindications

- History of severe hypersensitivity to irinotecan or hypersensitivity to any of the excipients of Camrata.
- Chronic inflammatory bowel disease and/or bowel obstruction (see Section 4.4).
- Pregnancy and lactation (see Section 4.6).
- Biliruibin > 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 or capecitabine, refer to the summary of product characteristics for these medicinal products.

4.4 Special warnings and precautions for use

The use of Camrata should be restricted to units specialised in the administration of cytotoxic chemotherapy and only under the supervision of a physician qualified in the use of anticancer chemotherapy. Given the adverse events profile of irinotecan it should only be prescribed in the following cases after consideration of the benefits having been weighed against the possible therapeutic risk:

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

When Camrata is used in monotherapy, it is usually prescribed with the every-3-week-dosage schedule. However, the weekly-dosage schedule (see Section 5) may be considered in patients who may need a closer follow-up or who are at particular risk of severe neutropenia.

Delayed diarrhoea:

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

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

As soon as the first liquid stools occur, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal treatment initiated immediately. This anti-diarrhoeal treatment will be prescribed by the department where the Camrata has been administered. After discharge from the hospital the patient should be provided with anti-diarrhoeal drugs so they can initiate treatment immediately it occurs. In addition, the patient must inform their physician or the department administering the Camrata when/if diarrhoea occurs.

A high dose of loperamide (4 mg for the first intake and then 2 mg every 2 hours) is the recommended anti-diarrhoeal treatment. Treatment should continue for 12 hours after passing the last liquid stool and should not be modified. In no instance should the 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 the diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm^3).

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 for patients who have experienced delayed diarrhoea on previous cycles.

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

Haematology:

Weekly monitoring of complete blood cell counts is recommended during treatment with Camrata. Patients should be informed of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature > 38ºC, neutrophil count ≤ 1,000 cells/mm^3) should be urgently treated in hospital with broad spectrum intravenous antibiotics. In patients who experienced severe haematological events, a dose reduction is recommended for subsequent cycles (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.

Liver impairment:

Liver function tests should be performed at baseline and before each cycle. In patients with bilirubin ranging from 1.5 to 3 times ULN weekly monitoring of complete blood counts should be conducted due to decrease of the clearance of irinotecan (see Section 5.2) and thus increasing the risk of haematoxicity in this population. Irinotecan treatment is contraindicated for patients with bilirubin > 3 times ULN (see Section 4.3).

Nausea and vomiting:

As nausea and vomiting have been frequently reported prophylactic treatment with antiemetics is recommended before treatment with Camrata. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment.

Acute cholinergic syndrome:

If acute cholinergic syndrome appears (early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0.25 mg 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.

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.

Elderly:

Dose selection with Camrata should be made with caution in the elderly due to decreased biological function, in particular hepatic function (see Section 4.2).

Patients with bowel obstruction:

Patients must not be treated with Camrata until resolution of the bowel obstruction (see Section 4.3).

Patients with impaired renal function:

No studies have been conducted in this population (see Sections 4.2 and 5.2).

Others:

As Camrata concentrate for solution for infusion contains sorbitol patients with rare hereditary problems of fructose intolerance should not be given this medicine. This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium- free'. In patients who experienced episodes of diarrhoea and/or vomiting, or sepsis, infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed. Contraceptive measures must be taken whilst taking Camrata and for at least 3 months after end of therapy. Concomitant administration of strong inhibitors or inducers of CYP3A4 (e.g. ketoconazole, rifampicin, carbamazepine, phenobarbitol, phenytoin, St John's Wort) 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. Irinotecan has anticholinesterase activity therefore 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 anticonvulsants drugs (e.g. carbamazepine, phenobarbital or phenytoin) leads to reduced exposure of irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effect 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 PA450 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 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 or induce drug metabolism by cytochrome P450 3A4 (e.g. ketoconazole, rifampicin, carbamazepine, phenobarbitol, phenytoin). Concurrent administration of Camrata 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 co-administered with St. John's Wort (Hypericum perforatum) 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentration was observed.

St John's Wort should not be administered with Camrata as it decreases SN-38 (an active metabolite of irinotecan (see Section 4.3).

Co-administration of 5-FU/FA acid in combination regimen does not change the pharmacokinetics of irinotecan.

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

More dose reductions of irinotecan were reported for patients receiving the bevacizumab in combination with irinotecan/5-FU/FA. Patients who develop severe diarrhoea, leucopenia, or neutropenia with the bevacizumab and irinotecan/5-FU/FA combination should have a modification of the Camrata dose as specified in Section 4.2.

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

4.6 Fertility, pregnancy and lactation

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, Camrata must not be used during pregnancy (see Sections 4.3 and 4.4).

Women of child-bearing potential:

Women of child-bearing age receiving Camrata should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur (see Sections 4.3 and 4.4).

Lactation:

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The information provided 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 undesirable effects were those expected with cetuximab (e.g. acneform rash 88%). Therefore also refer to the cetuximab summary of product characteristics.

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

Adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: *Very common, all grade adverse drug reactions:* thrombosis/embolism; *Common, all grade adverse drug reactions:* hypersensitivity reaction, cardiac ischemia/infarction; *Common, grade 3 and 4 adverse drug reactions:* febrile neutropenia. For complete information on adverse reactions of capecitabine, refer to the capecitabine summary of product characteristics.

Grade 3 and Grade 4 adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan and bevacizumab in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: *Common, grade 3 and grade 4 adverse drug reactions:* neutropenia, thrombosis/embolism, hypertension, and cardiac ischemia/infarction. For complete information on adverse reactions of capecitabine and bevacizumab, refer to the respective capecitabine and bevacizumab summary of product characteristics.

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

Gastrointestinal disorders:

Delayed diarrhoea:

Diarrhoea (occurring more than 24 hours after administration) is a dose-limiting toxicity of irinotecan.

In monotherapy:

Severe diarrhoea was observed in 20% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14% have a severe diarrhoea. The median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.

In combination therapy:

Severe diarrhoea was observed in 13.1% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9% have a 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: Nausea and vomiting were severe in approximately 10% of patients treated with antiemetics.

In combination therapy: lower incidence of severe nausea and vomiting was observed (2.1% and 2.8% of patients respectively).

Dehydration:

Episodes of dehydration commonly associated with diarrhoea and/or vomiting have been reported. Infrequent 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.

Other gastrointestinal disorders:

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.

Infrequent cases of intestinal obstruction, ileus, or gastrointestinal haemorrhage and rare cases of colitis, including typhlitis, ischemic and ulcerative colitis, were reported. Rare cases of intestinal perforation were reported. Other mild effects include anorexia, abdominal pain and mucositis.

Rare cases of symptomatic or asymptomatic pancreatitis have been associated with irinotecan therapy.

Blood 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 combination therapy.

In monotherapy: Neutropenia was observed in 78.7% of patients and severe (neutrophil count < 500 cells/mm^3) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count between 1,000 cells/mm^3 including 7.6% with a neutrophil count < 500 cells/mm^3. Total recovery was usually reached by day 22. Fever with severe neutropenia was reported in 6.2% of patients and in 1.7% of cycles.

Infectious episodes in about 10.3% of patients (2.5% of cycles) and were associated with severe neutropenia in about 5.3% patients (1.1% of cycles), and resulted in death in 2 cases.

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

Thrombocytopenia (< 100,000 cells/mm^3) 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 patients showed a recovery by day 22.

In combination therapy: 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/mm^3 including 2.7% with neutrophil count < 500 cells/mm^3. Total recovery was usually reached within 7 - 8 days. 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.

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

Thrombocytopenia (< 100,000 cells/mm^3) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (<50,000 cells/mm^3) has been observed. One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.

Infection and infestation:

Infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced sepsis.

General disorders and infusion site reactions:

Acute cholinergic syndrome:

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, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of irinotecan. 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 in monotherapy and in 6.2% of patients treated in combination therapy.

Mild infusion site reactions have been reported uncommonly.

Cardiac disorder:

Rare cases of hypotension during or following the infusion have been reported.

Respiratory disorders:

Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnoea have been reported (see Section 4.4)

Skin and subcutaneous disorders:

Alopecia was very common and reversible. Mild cutaneous reactions have been reported although uncommonly.

Immune system disorders:

Uncommon mild allergic reactions and rare cases of anaphylactic/anaphylactoid reactions have been reported.

Musculoskeletal disorders:

Early effects such as muscular contraction or cramps and parasthesia have been reported.

Laboratory tests:

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.

In combination therapy: Transient serum levels (grades 1 and 2) of either SGPT, SGOT, 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 was observed in 0%, 0%, 0% and 1% of the patients, respectively. No grade 4 was observed. Increases of amylase and/or lipase have been very rarely reported.

Rare cases of hypokalemia and hyponatremia mostly related with diarrhoea and vomiting have been reported.

Nervous system disorders:

There have been very rare reports of transient speech disorders associated with irinotecan infusions.

4.9 Overdose

There have been reports of overdosage at up to approximately twice the recommended therapeutic dose, which may be fatal. Most significant adverse reactions reported were severe neutropenia and severe diarrhoea. There is no antidote to Camrata, maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cytostatic topoisomerase I inhibitor
ATC Code: L01XX19

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-stranded DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxicity 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 P-glycoprotein MDR, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines. Furthermore, irinotecan has a broad antitumour 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 tumours expressing the P-glycoprotein MDR (vincristine- and doxorubicin-resistant P388 leukaemia's). Besides the anti-tumour activity of irinotecan, the most relevant pharmacological effect is the inhibition of acetylcholinesterase.

Clinical data

In combination therapy for the first-line treatment of metastatic colorectal carcinoma

In combination therapy with FA and 5-FU

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 at 180 mg/m^2 once every 2 weeks is followed by infusion with FA (200 mg/m^2 over a 2-hour intravenous) and 5-FU (400 mg/m^2 as an intravenous bolus, followed by 600 mg/m^2 over a 22-hour intravenous infusion). On day 2, FA and 5-FU are administered at the same doses and schedules. In the weekly schedule, the administration of irinotecan at 80 mg/m^2 is followed by infusion with FA (500 mg/m^2 over a 2-hour intravenous infusion) and then by 5-FU (2300 mg/m^2 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 + 5-FU/FA	5-FU/FA	Irinotecan + 5-FU/FA	5-FU/FA	Irinotecan + 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	6.7	4.4	7.2	6.5	6.5	3.7

progression (months)						
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	119.2	14.1	15.6	13.0
p value	p = 0.028		NS		p = 0.041	

5-FU: 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 5-FU/FA and 25.6% in patients with

5-FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500 cells/mm^3) was 5.8% in patients treated by irinotecan in combination with 5-FU/FA and 2.4% in patients treated by 5-FU/FA alone. Additionally, median time to definitive performance status deterioration was significantly longer in irinotecan combination than in 5-FU/FA alone group (p = 0.046).

Quality of life was assessed in this phase III study using the EORTC QLC-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 the efficacy of irinotecan in combination could be reached without affecting the quality of life.

In combination with bevacizumab:

A phase II randomised, double-blind, active-controlled clinical trial evaluated bevacizumab in combination with irinotecan/5-FU/FA as the first-line treatment for metastatic carcinoma of the colon or rectum (study AVF2107g). The addition of bevacizumab to the combination resulted in a statistically increase in overall survival. The clinical benefit, 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 to the bevacizumab summary of product characteristics. The efficacy results are summarised below.

	AVF2107g	
	Arm 1 Irinotecan/5-Fu/FA + placebo	Arm 2 Irinotecan/5-FU/FA + bevacizumab[a]
Number of patients	411	402
Overall survival		
Median time (months)	15.6	20.3
95% CI	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, CI confidence interval

In combination with cetuximab:

EMR 62 202-013: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and irinotecan plus infusional 5-FU/FA (599 patients) to the same chemotherapy alone (599 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 64%. The efficacy data generated in this study are summarised in the table below:

	Overall population		KRAS wild-type population	
Variable/statistic	Cetuximab + FOLFRI (n=599)	FOLFRI (n=599)(	Cetuximab + FOLFRI (n=172)	FOLFRI (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, FOLFRI irinotecan + infusional 5-FU/FA, ORR objective response rate (patients with complete response or partial response), PFS progression-free survival time

In combination therapy with capecitabine

Data from randomised, controlled phase III study (CARIO) support the use of capecitabine at a starting dose of 1000 mg/m^2 for 2 weeks every 3 weeks in combination with irinotecan 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 first-line treatment with capecitabine (1250 mg/m^2 twice daily for 14 days), second-line irinotecan (350 mg/m^2 on day 1), and third-line combination of capecitabine (1000 mg/m^2 twice daily for 14 days) with oxaliplatin (130 mg/m^2 on day 1). Combination treatment consisted of first-line treatment of capecitabine (1000 mg/m^2 twice daily for 14 days) combined with irinotecan ~(250 mg/m^2 on day 1) (XELRI) and second-line capecitabine (1000 mg/m^2 twice daily for 14 days) plus oxaliplatin (130 mg/m^2 on day 1). All treatment cycles were administered at intervals of 3 weeks. 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).

Data from 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 and bevacizumab for the 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 2 weeks followed by a 7-day rest period), irinotecan (200 mg/m^2 as a 30 minute infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg 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 2 weeks followed by a 7-day rest period), oxaliplatin (130 mg/m^2 as a 2 hour infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg As a 30 to 90 minute infusion on day 1 every 3 weeks). Progression-free survival at 6 months in the intent-to-treat population was 80% (XELRI plus bevacizumab) versus 74% (XELOX plus bevacizumab). Overall response rate (complete response plus partial response) was 45% (XELOX plus bevacizumab) versus 47% (XELIRI plus bevacizumab).

In monotherapy for the second-line treatment of metastatic colorectal carcinoma:

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 5-FU		
	Irinotecan n=183	Supportive care n=90	p-values	Irinotecan n=127	5-FU n=129	p-values
Progression free survival at 6 months (%)	n/a	n/a		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

n/a 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/m^2 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 weekly-dosage schedule in 193 patients at the starting dose of 125 mg/m^2, compared to the every 3-week-dosage schedule. The median time of onset of the first liquid stool was on day 11.

In combination with cetuximab after failure of irinotecan-including cytotoxic therapy

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 $\geq$ 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
IMCLCP02 -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 the 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).

Pharmacokinetic/Pharmacodynamic data:

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

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/m^2 every three weeks, irinotecan showed a biphasic or triphasic elimination profile. The mean plasma clearance was 15 L/h/m^2 and the volume of distribution at steady state (Vss): 157 L/m^2. 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/m^2, 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 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 and SN-38 exposure increase proportionally with irinotecan 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 derivative) and NPC (primary amine derivative) (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/m^2 irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m^2 in cancer patients with normal liver parameters.

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/m^2 (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 were reported. Alopecia was also observed in dogs. The severity of these effects was dose related and reversible.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Lactic acid
Sodium hydroxide and/or hydrochloric acid (for pH adjustment)
Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in Section 6.6.

6.3 Shelf Life

The shelf life of the unopened vial is 24 months.

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

Chemical and physical in-use stability has been demonstrated in 5% (w/v) glucose and 0.9% (w/v) sodium chloride for 48 hours at 2 - 8ºC and 24 hours at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2 – 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25ºC. Store in the original package in order to protect from light. For storage conditions of the diluted medicinal product, see Section 6.3.

6.5 Nature and contents of container

Camrata concentrate for solution for infusion is supplied as either 40 mg/2 ml or 100 mg/5 ml. in type I amber glass vial (2 ml or 5 ml), with a chlorobutyl rubber stopper coated with teflon on the inner surface with an aluminium shell and a blue plastic flip-off button .

Packs of 1 vial containing either 40 mg or 100 mg Camrata.

6.6 Special precautions for disposal

Must be diluted before use. For single use only. Any remaining solution should be discarded.

As with other antineoplastic agents, Camrata must be prepared and handled with caution. The use of glasses, mask and gloves is required. If Camrata concentrate solution or infusion solution come into contact with the skin, wash immediately and thoroughly with soap and water. If Camrata concentrate solution or infusion solution should come into contact with mucous membranes, wash immediately with water.

Preparation of the intravenous infusion administration:

As with other injectable drugs, Camrata solution must be prepared aseptically (see Section 6.3). If any precipitate is observed in the vials or after reconstitution, the product should be discarded according to the standard procedures for cytotoxic agents. Aseptically withdraw the required amount of Camrata solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 0.9% sodium chloride or 5% glucose solution. The infusion should then be thoroughly mixed by manual rotation.

Disposal:

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

7 MARKETING AUTHORISATION HOLDER

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10 DATE OF REVISION OF THE TEXT