PACKAGE INSERT FOR COLOCAM

SCHEDULING STATUS:

S4

PROPRIETARY NAME and dosage form:

COLOCAM 40 Concentrate for solution for infusion

COLOCAM 100 Concentrate for solution for infusion

COLOCAM 300 Concentrate for solution for infusion

COLOCAM 500 Concentrate for solution for infusion

COMPOSITION:

Each 1 ml contains 20 mg irinotecan hydrochloride.

COLOCAM 40 contains 40 mg irinotecan hydrochloride per vial.

COLOCAM 100 contains 100 mg irinotecan hydrochloride per vial.

COLOCAM 300 contains 300 mg irinotecan hydrochloride per vial.

COLOCAM 500 contains 500 mg irinotecan hydrochloride per vial.

Excipients: Sorbitol, lactic acid, water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 26. Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Irinotecan is a camptothecin analogue which forms part of antineoplastic medicine that acts as a specific inhibitor of nuclear enzyme topoisomerase I. This DNA topoisomerases are nuclear enzymes that reduce supercoiled DNA torsional stress, allowing selected regions of DNA to become sufficiently untangled and relaxed to permit its replication, recombination, repair and transcription. Topoisomerase I binds covalently to double-stranded DNA through a reversible

trans-esterification reaction. This reaction yields an intermediate complex in which the tyrosine of the enzyme is bound to the 3′-phosphate end of the DNA strand, creating a single-strand DNA break. This “cleavable complex” allows for relaxation of the DNA torsional strain, either by passage of the intact single-strand through the nick, or by free rotation of the DNA about the noncleaved strand.

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

Pharmacokinetic properties:

Irinotecan exhibits biphasic or triphasic pharmacokinetics. After intravenous doses it is hydrolysed by carboxylesterase to active SN-38. SN-38 exhibits a biphasic elimination profile with a terminal half-life of about 14 hours. Plasma protein binding for irinotecan and SN-38 is about 65 % and 95 % respectively. SN-38 is mainly eliminated by glucuronidation, predominantly by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Irinotecan is also partly metabolised by cytochrome P450 isoenzymes CYP3A4 and perhaps CYP3A5. More than 50 % of an intravenous dose of irinotecan is excreted unchanged, with about 30 % in the faeces via the bile and about 20 % in the urine.

INDICATIONS

COLOCAM is indicated for the treatment of patients with advanced colorectal cancer with a WHO performance status of 2 or lower:

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

CONTRAINDICATIONS

COLOCAM is contra-indicated in the following:

- Patients with a history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of COLOCAM.
- Pregnancy and lactation. See “Pregnancy and Lactation”.
- Chronic inflammatory bowel disease, and/or bowel obstruction or ileus.
- Patients should not be treated with COLOCAM until resolution of the ileus.
- Bilirubin > 1,5 times the upper limit of the normal range.
- Severe bone marrow failure.
- WHO performance status > 2.
- Concomitant use with St. John’s Wort (see “INTERACTIONS”).

WARNINGS and SPECIAL PRECAUTIONS

The safety and efficacy of COLOCAM in children have not been established.

COLOCAM should be used in patients with a good performance status of less than 2 (see “CONTRAINDICATIONS”).

The use of COLOCAM should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered to patients under the supervision of a medical practitioner with experience in anticancer chemotherapy.

Equipment and medicines necessary for treatment of complications should be readily available (including an intensive care unit).

Premedication with anti-emetic agents are recommended in order to reduce nausea and vomiting associated with COLOCAM treatment. This treatment should be started at least 30 minutes before the infusion. In all instances where the use of COLOCAM is considered for chemotherapy, it is especially important to ensure that the patient understands the need for sufficiently prolonged anti-diarrhoeal treatment and abundant fluid intake. If severe diarrhoea or other toxicity occurs, further treatment should be withheld until recovery occurs.

Strict follow-up of the patient by the treating medical practitioner or hospitalisation is

recommended in rare cases where it is predictable that the patient would comply poorly with the guidance for the management of side effects of COLOCAM.

Given the nature and frequency of adverse events, the expected benefit must be balanced in case of risk factors, especially WHO Performance status ≥ 2 (or Karnofsky Index < 50).

Delayed diarrhoea:

There is a high risk of delayed diarrhoea occurring more than 24 hours after the administration of COLOCAM, which can be life-threatening (especially if the patient is concomitantly neutropenic).

In monotherapy, the onset of the first liquid stool is approximately 5 days after the infusion of COLOCAM. Patients should immediately inform their medical practitioner and start appropriate therapy.

Patients with an increased risk of diarrhoea:

- Patients who had previous abdominal/pelvic radiotherapy,
- Patients with baseline hyperleukocytosis and
- Patients with performance status ≥ 2.

Large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal therapy must be initiated immediately after the first liquid stool occurs.

Anti-diarrhoeal treatment will be prescribed by the medical practitioner. After discharge from the hospital the patients should obtain the prescribed medicine so that they can treat the diarrhoea as soon as it occurs. The treating medical practitioner or the department administering COLOCAM should be notified that diarrhoea is occurring.

The currently recommended anti-diarrhoeal treatment is loperamide 4 mg for the first intake and then 2 mg every 2 hours. This therapy should continue for 12 hours after the last liquid stool and should not be modified. Loperamide should not be administered for more than 48 consecutive hours at these doses (because of the risk of paralytic ileus) nor for less than 12 hours.

A prophylactic broad spectrum antibiotic should be given concomitantly with the anti-diarrhoeal treatment if 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.
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.
- Severe diarrhoea (requiring intravenous hydration).

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

A COLOCAM dose reduction is recommended for subsequent cycles in patients who experienced severe diarrhoea.

Haematology:

Patients who develop leukopenia should be observed carefully for signs and symptoms of infection. Patients should be aware of the risk of infection and the significance of a fever. In neutropenic patients who develop fever, broad spectrum antibiotic coverage should be initiated empirically, pending bacterial cultures and appropriate diagnostic tests. Febrile neutropenia (temperature ≥ 38 °C and neutrophil count ≤ 1 000 cells/mm^3) should be urgently treated in the hospital with broad spectrum intravenous antibiotics. COLOCAM treatment should be delayed until the neutrophil count is ≥ 1 500 cells/mm^3. The COLOCAM dose should be reduced in patients who experienced severe asymptomatic neutropenia (< 500 cells/mm^3; fever or infections associated with neutropenia).

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea.

Liver impairment:

COLOCAM should not be used in patients with a bilirubin >1,5 times the upper limit of the normal (ULN) and the patients with bilirubin > ULN should be followed with caution. Patients with impaired liver function (bilirubin > 1,0 times and ≤ 1,5 times the ULN and transaminases 5 times ULN) are at greater risk of developing severe neutropenia or febrile neutropenia and should be closely monitored.

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

Nausea and vomiting:

Nausea and vomiting have been frequently reported. Prophylactic treatment with an anti-emetic is recommended before each treatment with COLOCAM. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment. See "Delayed diarrhoea" section.

Acute cholinergic syndrome:

Acute cholinergic syndrome (defined as early diarrhoea and a group of symptoms such as sweating, myosis, lacrimation, abdominal cramping, and salivation), should be treated with atropine sulphate (0,25 mg subcutaneously) unless clinically contra-indicated. Caution is advised in patients with asthma. If acute cholinergic syndrome was reported, the use of prophylactic atropine sulphate is recommended with subsequent doses of COLOCAM.

Immunosuppressant effect:

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including COLOCAM, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving COLOCAM (see "INTERACTIONS"). Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Respiratory disorders:

Interstitial pulmonary disease presenting as pulmonary infiltrates may occur less frequently during COLOCAM therapy. Interstitial pulmonary disease can be fatal.

Risk factors possibly associated with the development of interstitial pulmonary disease include the use of pneumotoxic medicines, radiation therapy and colony stimulating factors.

Patients with risk factors should be closely monitored for respiratory symptoms before and during COLOCAM therapy.

Excipients:

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

Effects on ability to drive and use machines:

Patients should be warned about the potential for dizziness or visual disturbances, and advised not to drive or operate machinery if these symptoms occur.

Elderly:

COLOCAM should be administered with caution in the elderly due to the greater frequency of decreased hepatic, renal or cardiac function.

Others:

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

INTERACTIONS

St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be taken with COLOCAM (see "CONTRAINDICATIONS").

Vaccines: Yellow fever vaccine: There is a risk of fatal generalised reaction to vaccines. Concomitant use with COLOCAM (see "WARNINGS and SPECIAL PRECAUTIONS").

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

Atazanavir sulphate. Co-administration of atazanavir sulphate, a CYP3A4 and UGT1A1 inhibitor, may increase systemic exposure to SN-38, the active metabolite of irinotecan. Medical

practitioners should take this into consideration when co-administering these medicines.

Additive bone marrow depression may occur; dosage reductions may be required if COLOCAM and other bone marrow depressants or radiation therapy is administered concomitantly.

Concurrent therapy with COLOCAM and diuretics can lead to an increased severity of dehydration associated with irinotecan-induced diarrhoea or vomiting.

There is an increased risk of infection if COLOCAM and immunosuppressants (ciclosporin, tacrolimus, azathioprine, chlorambucil, coritcosteroids etc.) are administered concurrently.

Due to an increased risk of severe diarrhoea, laxatives should not be used during COLOCAM treatment.

Pharmacokinetic parameters of COLOCAM combined with 5-fluorouracil-folinic acid are comparable to those observed in monotherapy.

Interaction between COLOCAM and neuromuscular blocking agents cannot be ruled out. Medicines with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising agents may be antagonised.

PREGNANCY AND LACTATION

COLOCAM is contra-indicated in pregnancy and lactation.

Women of childbearing age receiving COLOCAM should be advised to avoid becoming pregnant and to inform the treating medical practitioner immediately should this occur.

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

DOSAGE AND DIRECTIONS FOR USE:

Recommended dosage:

In monotherapy (for a previously treated patient):

The recommended dosage of COLOCAM is 350 mg/m^2 administered as an intravenous infusion over a 30 minute to 90 minute period every three weeks.

In combination therapy (for a previously untreated patient)

Safety and efficacy of COLOCAM in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with either of the following schedules:

- **COLOCAM plus 5FU/FA in weekly schedule:**

  The recommended dose of COLOCAM is 80 mg/m^2 administered as a weekly intravenous infusion (IV) over a 30 to 90 minute period, followed by infusion with folinic acid and then by 5-fluorouracil over 6 weeks. This treatment is followed by one week rest.

  The full dosage regimen is as follows:

  COLOCAM 80 mg/m^2 as a 30 to 90 minute infusion on Day 1 and then weekly for 6 weeks.

  Folinic acid 500 mg/m^2 IV as a 2 hour infusion, followed by

  5-fluorouracil 2 000 mg/m^2 IV as a 24-hour infusion, on Day 1 and then weekly for 6 weeks.

  The treatment is to be repeated every 7 weeks.

- **COLOCAM plus 5FU/FA every 2 weeks schedule:**

  The recommended dose of COLOCAM is 180 mg/m^2 administered once every 2 weeks as an intravenous infusion (IV) over a 30 to 90 minute period, followed by infusion with folinic acid and 5-fluorouracil.

  The full dosage regimen is as follows:

  COLOCAM 180 mg/m^2 IV as a 30 to 90 minute infusion on Day 1 only.

  Folinic acid 200 mg/m^2 IV as a 2-hour infusion, followed by

  5-fluorouracil 400 mg/m^2 IV bolus, followed by 5-fluorouracil 600 mg/m^2 IV as a 22 hour infusion. The folinic acid and 5-fluorouracil are repeated for two consecutive days.

  Repeat the cycle every two weeks.

Dosage adjustments:

Delayed dosing:

COLOCAM should not be administered until the neutrophil count remains above 1500 cells/mm^3.

In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of COLOCAM should be delayed until there has been a full recovery of these effects, especially diarrhoea.

COLOCAM 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. This must be strictly adhered to.

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

With the following adverse events a dose reduction of 15 to 20 % should be applied for COLOCAM and/or 5FU when applicable:

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

Treatment duration:

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

Special populations:

Impaired hepatic function:

Frequent monitoring of complete blood counts should be conducted in patients with impaired liver function. Patients with a bilirubin > 1,5 times the ULN (upper limit of the normal range) should not

be treated with COLOCAM. In patients with a bilirubin ≤ 1,5 times the ULN range, a dose of 350 mg/m^2 COLOCAM is recommended. In patients with bilirubin > 1 and ≤ 1,5 times the ULN, the risk of severe neutropenia is increased.

Elderly:

The dose should be chosen carefully in this population due to their greater frequency of decreased hepatic, renal of cardiac function.

Preparation for the Intravenous Infusion Administration:

Aseptically withdraw the required amount of COLOCAM solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 0,9 % sodium chloride solution or 5 % dextrose solution. The infusion should then be thoroughly mixed by manual rotation. COLOCAM infusion solution should be infused into a peripheral or central vein.

COLOCAM should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes. If any precipitate is observed in the vials before or after reconstitution, the product should be discarded according to standard procedures for cytotoxic agents. After dilution with either 0,9 % sodium chloride or 5 % dextrose solution, the diluted solution is stable for 24 hours under refrigeration (2 – 8 °C) and for 6 hours when stored at room temperature (25 °C).

Do not admix with other medicines.

Recommendations for safe handling:

Medicine handling precautions for cytostatic medicine should be followed:

- Only trained personnel should reconstitute COLOCAM in a designated area.
- COLOCAM is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing COLOCAM solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If COLOCAM solution or infusion should come into contact with the skin, wash immediately

and thoroughly with soap and water. If COLOCAM solution or infusion solution should come in contact with the eyes or mucous membranes, wash immediately and thoroughly with water.

- The cytotoxic preparation must not be handled by pregnant staff.
- Adequate care and precautions should be taken in the disposal of items used to reconstitute COLOCAM.

SIDE EFFECTS

Blood and the lymphatic system disorders

Frequent: Anaemia, leukopenia, neutropenia.

Less frequent: Thrombocytopenia.

Frequencies not known: Peripheral thrombocytopenia with antiplatelet antibodies has been reported.

Immune system disorders

Less frequent: Hypersensitivity reactions, including anaphylactic, anaphylactoid reactions.

Metabolism and nutrition disorders

Frequent: Decrease or loss in appetite, weight loss.

Nervous system disorders

Frequent: Acute cholinergic syndrome (early diarrhoea, abdominal pain, conjunctivitis, hypotension, vasodilation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lacrimation and increased salivation within 24 hours after the infusion of COLOCAM) (see “WARNINGS and SPECIAL PRECAUTIONS”).

Less frequent: Paraesthesia.

Vascular disorders

Less frequent: Hypertension.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea.

Less frequent: Upper respiratory tract infection, rhinitis, interstitial pneumonia (see "WARNINGS and SPECIAL PRECAUTIONS").

Gastrointestinal disorders:

Frequent: Diarrhoea (possibly preceded by abdominal cramping and/or sweating), abdominal cramps or pain, constipation, nausea and vomiting, episodes of dehydration commonly associated with diarrhoea (see "WARNINGS and SPECIAL PRECAUTIONS").

Less frequent: Intestinal obstruction, ileus or gastrointestinal haemorrhage, intestinal perforation, transient increase in amylase and lipase, anorexia, mucositis, abdominal enlargement, bloated feeling or gas, *Clostridium difficile* induced pseudo-membranous colitis, indigestion.

Skin and subcutaneous tissue disorders

Less frequent: Skin rash, alopecia, mild cutaneous reactions.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Muscular contraction or cramps.

Renal and urinary disorders

Less frequent: Renal insufficiency.

General disorders and administrative site conditions

Frequent: Fever, neutropenic fever, asthenia.

Less frequent: Oedema, headache, increased sweating, stomatitis, vasodilation (flushing), infusion site reactions.

Frequency not known: Transient speech disorders.

Investigations

Frequent: Monotherapy: transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatise, bilirubin and creatinine.

Combination therapy: transient increases in serum levels (grades 1 and 2) of either SGPT, SGOT, alkaline phosphatase or bilirubin.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal.

Symptoms: The most significant adverse reactions reported were severe neutropenia and diarrhoea.

Treatment: There is no known antidote for COLOCAM. It is recommended that the patients be hospitalised for close monitoring of vital functions and treatment of observed effects. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

IDENTIFICATION

Clear, yellow solution.

PRESENTATION

COLOCAM 40: Amber Type I glass vial (2R) with grey halobutyl teflon coated rubber stopper and aluminium cap with red polypropylene flip-off seal.

COLOCAM 100: Amber Type I glass vial (6R) with grey halobutyl teflon coated rubber stopper and aluminium cap with yellow polypropylene flip-off seal.

COLOCAM 300: Amber Type I glass vial (20R) with grey halobutyl teflon coated rubber stopper and red aluminium cap with orange polypropylene flip-off seal.

COLOCAM 500: Amber Type I glass vial (30R) with grey halobutyl teflon coated rubber stopper and red aluminium cap with red polypropylene flip-off seal.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light.

Store the vials in the original cartons until required for use.

After dilution with either 0,9 % sodium chloride or 5 % dextrose solution, the diluted solution is stable for 24 hours under refrigeration (2 – 8 °C) and for 6 hours when stored at room temperature (25 °C).

Solution should be inspected visually for particulate matter and discoloration prior to administration.

Procedures for proper handling and disposal of anti-cancer medicines should always be considered.

Discard any unused portion thereafter.

Do not freeze as crystallisation may occur.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

Colocam 40: 46/26/0271

Colocam 100: 46/26/0272

Colocam 300: 46/26/0273

Colocam 500: 46/26/0274

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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