VI.2 Elements for a public summary

Capecitabine Orion is an anticancer medicine. It is used either alone or together with other anticancer medications in the treatment of:

- large-bowel cancer.
- cancer of the large bowel and rectum that has spread to other parts of the body (metastatic colorectal cancer)
- advanced stomach cancer
- breast cancer that has begun to spread to other parts of the body (locally advanced or metastatic breast cancer).

VI.2.1 Overview of disease epidemiology

Bowel cancer is a general term for cancer that begins in the large bowel. Depending on where the cancer starts, bowel cancer is sometimes called colon cancer or rectal cancer. Approximately 72% of bowel cancer cases develop in people who are 65 or over. Two-thirds of bowel cancers develop in the colon, with the remaining third developing in the rectum.

Stomach cancer is a relatively uncommon cancer. Men are twice as likely to be affected as women. The average age at diagnosis for men is 70 years and 74 years for women.

Breast cancer is a common form of cancer. Most of the patients (eight out of 10) are over 50, but younger women, and in rare cases, men, can also get breast cancer.

Invasive breast cancer is a type of cancer that has the ability to spread outside the breast. The most common form is invasive ductal breast cancer. Invasive ductal breast cancer accounts for about 80% of all cases of breast cancer.

Metastatic cancer is cancer that has spread from the place where it first started to another place in the body. The most common sites of cancer metastasis are the lungs, bones, and liver.

VI.2.2 Summary of treatment benefits

Capecitabine Orion belongs to the group of medicines called "cytostatic medicines", which stop the growth of cancer cells. The active ingredient is capecitabine, which itself is not a cytostatic medicine. Only after being absorbed by the body is it changed into an active anti-cancer medicine 5-fluorouracil (5-FU). More conversion to 5-FU is made in tumour tissue than in normal tissue.

5-FU is an analogue of pyrimidine. Pyrimidine is part of the genetic material of cells (DNA and RNA). In the body, 5-FU takes the place of pyrimidine and interferes with the enzymes involved in making new DNA. As a result, it inhibits the growth of tumour cells and eventually kills them.

Capecitabine is taken as tablets, while 5-FU normally needs to be injected.

VI.2.3 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Adverse effects on alimentary canal	Capecitabine can induce the occurrence of diarrhoea, which has been observed in up to 50% of patients.	• Careful monitoring of the patient • Administration of fluid and electrolyte replacement if necessary • Antidiarrhoeal medication

Risk	What is known	Preventability
		(e.g. loperamide) may be used. • Dose reduction of capecitabine, if necessary.
Hand-foot syndrome	Possible adverse reaction with different grades of severity. Grade 1 hand-foot syndrome is defined as numbness, dysesthesia/paresthesia, tingling, painless swelling or redness of the hands and/or feet and/or discomfort which does not disrupt the patient's normal activities. Grade 2 hand-foot syndrome is defined as painful redness and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-foot syndrome is moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. Persistent or severe hand-foot syndrome (Grade 2 and above) can eventually lead to loss of fingerprints which could impact patient identification.	• Careful monitoring of the patient • If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. • Following grade 3 hand-foot syndrome, the following doses of capecitabine should be decreased.
Adverse effects on heart	Heart rhythm disorders, chest pain (angina pectoris), heart attack, heart failure and heart muscle disease have been reported in patients receiving capecitabine. These adverse reactions may be more common in patients with a prior history of coronary artery	• Careful monitoring of the patient • Patients with history of significant coronary artery disease, rhythm disorders, angina pectoris and heart muscle disease are treated with special caution.

Risk	What is known	Preventability
	disease.	
Adverse effects on blood vessels	Lower limb oedema, high or low blood pressure, blood clots, flushing, hot flush and venous inflammation have been reported in patients receiving capecitabine.	• Careful monitoring of the patient and enquiry of patient's medical history to identify possible risk factors
Increased capecitabine toxicity with concomitant administration of sorivudine or analogues	Increased capecitabine toxicity as a result of this interaction may potentially cause death of the patient.	• Capecitabine must not be used concomitantly with sorivudine or its chemically related analogues, such as brivudine. • There must be at least a 4 weeks waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy.
Increased risk for capecitabine toxicity in patients with dihydropyrimidine dehydrogenase deficiency (DPD deficiency)	DPD deficiency is a rare condition of certain enzyme deficiency present at birth that is not usually associated with health problems unless patient receives certain medicines. If the patient has an unrecognised DPD deficiency and take capecitabine, he/she may experience severe forms of the side effects and even life-threatening toxicities manifesting as acute overdose.	• Capecitabine must not be used in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.
Spasm of blood vessel (coronary and peripheral vasospasm)	Vasospasm has been reported in patients receiving capecitabine.	• Careful monitoring of the patient and enquiry of patient's medical history to identify possible risk factors
Safety in patients who have kidney problems (Safety in patients with pre-existing compromised renal function)	Poorly functioning kidneys increase risk for undesirable effects.	• Reduced dose in patients with poorly functioning kidneys • Capecitabine must not be used in patients who have severely impaired kidney function
Adverse effect on cornea (eye's outermost layer: cornea) (Corneal disorder)	Corneal disorders have been reported in patients receiving capecitabine.	• Careful monitoring of the patient and enquiry of patient's medical history to identify possible risk factors
Severe skin reactions [Severe	Severe skin reactions such as	• Careful monitoring of the

Risk	What is known	Preventability
cutaneous adverse reactions (SCARs)]	Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported in patients receiving capecitabine. In those reactions skin and mucous membranes react severely to a medication. SJS and TEN presents a medical emergency that usually requires hospitalization.	patient and enquiry of patient's medical history to identify possible risk factors • Capecitabine should be permanently discontinued in patients who experience a severe skin reaction during treatment.
Photosensitivity reactions	Photosensitivity reactions have been reported in patients receiving capecitabine.	• Strong sunlight, solarium and UV therapy should be avoided during capecitabine therapy

Missing information

Risk	What is known
Safety in patients with liver impairment	Insufficient safety and efficacy data are available in patients with liver impairment to provide a dose adjustment recommendation. No information is available on liver impairment due to cirrhosis or hepatitis. Capecitabine must not be used in patients with severe liver impairment.
Use in pregnant and breastfeeding women	There are no studies in pregnant women using capecitabine; however, it should be assumed that capecitabine may cause foetal harm if administered to pregnant women. In reproductive toxicity studies in animals, capecitabine administration caused embryolethality and teratogenicity. These findings are expected effects of fluoropyrimidine derivatives. Capecitabine should not be used during pregnancy. It is not known whether capecitabine is excreted in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were found in milk. Breastfeeding should be discontinued while receiving treatment with capecitabine
Use in children	There is no relevant use of capecitabine in the paediatric population in the indications colon, colorectal, gastric and breast cancer.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in

the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Capecitabine Orion can be found in the local authority's web pages.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
1.1	08/08/2013	Important identified risks: • GI toxicity • Palmar-plantar erythrodysesthesia (HFS) • Cardiac toxicity • Vascular disorders • Increased capecitabine toxicity with concomitant administration of sorivudine or analogues • Toxicity in patients with DPD deficiency • Coronary and peripheral vasospasm Important potential risks: • Pancreatitis • Stevens-Johnson syndrome • Bullous dermatitis Important missing information: • Safety in patients with hepatic impairment • Use in pregnant	First approved version of the RMP.

Version	Date	Safety Concerns	Comment
		and lactating women • Use in children	
2.1	9.11.2016	Important identified risks: • GI toxicity • Palmar-plantar erythrodysesthesia (HFS) • Cardiac toxicity • Vascular disorders • Increased capecitabine toxicity with concomitant administration of sorivudine or analogues • Toxicity in patients with DPD deficiency • Coronary and peripheral vasospasm • Safety in patients with pre-existing compromised renal function • Corneal disorder • Severe cutaneous adverse reactions (SCARs) • Photosensitivity reactions Missing information: • Safety in patients with hepatic impairment • Use in pregnant and lactating women • Use in children	Changes made: • Safety concerns modified based on originator RMP • RMP modified based on updated product information • Technical editing of the RMP • Attached SmPC and PIL replaced with cross reference to the dossier section 1.3.1