VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

COLON/COLORECTALCANCER

Colorectal cancer (CRC) is one of the most common cancers worldwide and a prevalent cause of morbidity and mortality. CRC is a worldwide public health problem, with nearly 800,000 new cases diagnosed each year, resulting in approximately 500,000 deaths. When advanced metastatic disease is diagnosed, CRC is associated with a poor prognosis, and 5-year survival rates are in the range of 5%-8%. Chemotherapy has been the mainstay approach for patients with advanced CRC. CRC has a natural history of transition from a precursor lesion, i.e. adenomatous polyp to cancer that spans over 10 to 15 years providing an extended opportunity for intervention and cancer prevention.

Some patients have a genetic predisposition to developing colon cancer, which can result from certain hereditary diseases. Patients who have had adenomatous polyps have an increased risk of developing colon cancer.

GASTRICCANCER

Gastric cancer is the second most common cause of cancer-related death in the world, and it remains difficult to cure in Western countries, primarily because most patients present with advanced disease. Chronic inflammation, exposure to diverse carcinogens, and genetic susceptibility are among factors associated with an increased risk of gastric cancer. Chronic H. pylori infection is the most important cause of distal gastric adenocarcinoma. Smoking and dietary habits (high intake of salt-preserved and/or smoked foods) also play a role in increasing cancer risk, either individually or by compounding the role of H. pylori infection. Some individuals are at increased risk of developing gastric cancer due to genetic susceptibility.

For advanced gastric cancer, there is no doubt that gastrectomy with regional lymph node dissection is the only treatment modality. Multimodal treatment involving chemotherapy or radiotherapy in addition to surgery is thought to be a promising strategy for improving locoregional control of gastric cancer.

BREASTCANCER

Worldwide, breast cancer is the most common invasive cancer in women. Breast cancer incidence is highest in North America and Northern Europe and lowest in Asia and Africa. Studies of migration patterns suggest that genetic factors alone do not account for the incidence variation among countries. Breast cancer occurs 100 times more frequently in women than men. Familial breast cancer is considered a risk if a first-degree relative develops breast cancer before menopause. A woman's hormonal history appears to be a risk factor, as the relative risk of breast cancer seems to be related to the breast's cumulative exposure to estrogen and progesterone. Lifestyle conditions (obesity, lack of exercise, alcohol use), as well radiation are also risk factors for breast cancer.
The treatment of locally advanced breast cancer requires a combination of systemic chemotherapy, surgery, and radiotherapy to optimize the chance of cure.

VI.2.2 Summary of treatment benefits

- COLON/COLORECTALCANCER

Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer and for the treatment of metastatic CRC.

- GASTRICCANCER

Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen.

- BREASTCANCER

Capecitabine in combination with docetaxel is indicated for the treatment of patients with locally advanced breast cancer or metastatic breast cancer (MBC) after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or MBC after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

VI.2.3 Unknowns relating to treatment benefits

Treatment benefits of capecitabine in children (under 18 years of age) are not known, since there is no experience in this population.

Moreover, insufficient safety and efficacy data are available in patients with hepatic impairment. In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. According to a

pharmacokinetic study in cancer patients with mild to moderate liver impairment due to liver metastases, the bioavailability of capecitabine and exposure to 5-FU may increase compared to patients with no liver impairment. There are no pharmacokinetic data on patients with severe hepatic impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Cardiac disorders (cardiac toxicity): Angina unstable Angina pectoris Myocardial ischaemia Atrial fibrillation Arrhythmia Tachycardia / Cardiomyopathy Cardiac failure Sudden death Ventricular fibrillation QT prolongation Torsade de pointes	Cardiac disorders are uncommon side effects of capecitabine monotherapy.	Not known
Vascular disorders: Thrombophlebitis Deep vein thrombosis	Thrombophlebitis is a common side effect of capecitabine monotherapy, while deep vein thrombosis is uncommon.	Not known

Gastrointestinal disorders (GI toxicity): Gastrointestinal haemorrhage Intestinal obstruction Ascites Enteritis Gastritis Oesophagitis Colitis	Gastrointestinal haemorrhage is a common side effect of capecitabine monotherapy, while the rest respiratory disorders are uncommon.	Not known
Interaction with other medicinal products: Increased capecitabine toxicity with concomitant administration of sorivudine or analogues	A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.	Capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy.
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome	Not known

Risk	**What is known**	**Preventability**
Palmar-plantar erythrodysaesthesia syndrome	(also known as hand-foot skin reaction) is a very common side effect of capecitabine	
Toxicity in patients with Dihydropyrimidine dehydrogenase (DPD) deficiency	In patients with unrecognised DPD deficiency treated with capecitabine, life-threatening toxicities manifesting as acute overdose may occur.	Patients with known DPD deficiency should not be treated with capecitabine.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Pancreatitis	There have been reported 2 cases of pancreatitis after capecitabine use within the worldwide scientific literature [1, 2]. The MAH will continue to monitor this event.
Steven-Johnson Syndrome	There has been reported 1 case of Steven-Johnson Syndrome after capecitabine use within the worldwide scientific literature [3]. The MAH will continue to monitor this event.
Bullous dermatitis	It is known that capecitabine administration can cause skin and subcutaneous tissue disorders and bullous dermatitis is a potential skin disorder. The MAH will continue to monitor this event.

Important missing information

Risk	**What is known**
Pediatric patients (below 18 years of age)	There is no experience with administration of capecitabine in children below 18 years of age.
Hepatic impairment	Insufficient safety and efficacy data are available in patients with hepatic impairment to provide a dose adjustment recommendation.

Use in pregnant and lactating 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. It is not known whether capecitabine is excreted in human breast milk and there is no data on capecitabine and impact on fertility.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

VI.2.6 Planned post authorisation development plan

Not applicable

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

Not applicable

Capecitabin Fair-Med