TECHNICAL SHEET

1.NAME OF THE MEDICINAL PRODUCT

Capecitabine Normon 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg

of capecitabine.Excipients with known

effect
Each film-coated tablet contains 52 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Capecitabine Normon 500 mg film-coated tablets are light peach colored, oblong shaped tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ÿ Capecitabine is indicated for the treatment:

ÿ adjuvant after surgery in patients with stage III colon cancer (Dukes stage C) (seesection 5.1).

ÿ metastatic colorectal cancer (see section 5.1).

ÿ in first line of advanced gastric cancer in combination with a regimen that includes platinum (see section 5.1).

ÿ in combination with docetaxel (see section 5.1) for the treatment of patients with locally advanced or metastatic breastcancer after failure of cytotoxic chemotherapy. Prior therapy must have included an anthracycline.

ÿ as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and a chemotherapy regimen including an anthracycline or for those patients in whom further therapy with anthracyclines is not indicated.

4.2. Dosage and method of administration

Capecitabine should only be prescribed by a clinician experienced in the use of medications antineoplastic agents. Careful monitoring is recommended for all patients during the first cycle of treatment.

Treatment should be discontinued if progressive disease or intolerable toxicity occurs. Standard and reduced dose calculations based on body surface area for starting doses of capecitabineof 1,250 mg/m2 and 1,000 mg/m2 are shown in Tables 1 and 2, respectively.

Posology

Recommended dosage (see section 5.1).

Monotherapy
Colon, colorectal and breast cancer The
recommended starting dose of capecitabine when administered as monotherapy in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or locally advanced or metastatic breast cancer is 1,250 mg/m2 administered twicedaily (morning and evening; equivalent to a total daily dose of 2,500 mg/m2) for 14 days followed by a 7-day rest period. The recommended duration of adjuvant treatment in patients with stage III colon cancer is 6 months.

Combination treatment Colon,
colorectal and gastric cancer In combination
treatment, the recommended starting dose of capecitabine should be reduced to 800 – 1000 mg/m2 when administered twice daily for 14 days followed by a 7-day rest period, or to 625 mg/m2 twice daily when administered continuously (see section 5.1).
In combination with irinotecan, the recommended starting dose is 800 mg/m2 when administered twice daily for 14 days followedby a 7-day rest period and in combination on day 1 with irinotecan 200 mg/m2. The inclusion of bevacizumab in a combination regimen does not influence the starting dose of capecitabine.

For patients receiving capecitabine in combination with cisplatin, premedication to maintain hydration and appropriate antiemetic therapy, according to the cisplatin prescribing information, should be initiated prior tocisplatin administration. For patients receiving capecitabine in combination with oxaliplatin, antiemetic premedication is recommended, according to the oxaliplatin prescribing information. For patients with stageIII colon cancer, adjuvant treatment for 6 months is recommended.

Breast cancer In
combination with docetaxel, the recommended starting dose of capecitabine for the treatment of metastatic breast cancer is 1,250 mg/m2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at a dose of 75 mg/m2 as an intravenous infusion, administered over 1 hour, every 3 weeks. According to the SmPC for docetaxel, premedication with anoral corticosteroid, such as dexamethasone, should be started before administering docetaxel to patients treated with the capecitabine plus docetaxel combination.

Capecitabine Normon dose calculation

Table 1 Calculation of standard and reduced dose based on body surface area for a starting dose ofcapecitabine of 1250 mg/m2

Dose level 1250 mg/m2 (twice daily)			
Full dose 1250 mg/m2	Number of 150 mg tablets and/or 500 mg tablets per administration (each dose must be administered in the morning and at night)	Reduced dose (75%)	Reduced dose (50%)
		950 mg/m2	625 mg/m2

Body surface area (m2)	Dose per administration (mg)	150 mg mg	500		Dose per administration (mg)	Dose per administration (mg)
ÿ1.26	1500	-		3	1150	800
1.27 - 1.38	1650	1		3	1300	800
1.39 - 1.52	1800	2			1450	950
1.53 - 1.66	2000	-		3 4	1500	1000
1.67 - 1.78	2150	1		4	1650	1000
1.79 - 1.92	2300	2		4	1800	1150
1.93 - 2.06	2500	-		5	1950	1300
2.07 - 2.18	2650	1		5	2000	1300
ÿ2.19	2800	2		5	2150	1450

Table 2 Calculation of the standard and reduced dose according to body surface area for an initial dose ofcapecitabine 1000 mg/m2

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	Dose level 1000 mg/m2 (twice daily)				
Body surface area (m2)	Dose per administration (mg)	Number of tablets of 150 mg and/or tablets of 500 mg per administration (each take must be managed by the tomorrow and in the evening)		Dose per administration (mg)	Dose per administration (mg)
		150 mg	500 mg		
ÿ1.26	1150	1	2	800	600
1.27 - 1.38	1300	2	2	1000	600
1.39 - 1.52	1450	3	2	1100	750
1.53 - 1.66	1600	4	2	1200	800
1.67 - 1.78	1750	5	2	1300	800
1.79 - 1.92	1800	2	3	1400	900
1.93 - 2.06	2000	-	4	1500	1000
2.07 - 2.18	2150	1	4	1600	1050
ÿ2.19	2300	2	4	1750	1100

Dosage adjustments during treatment:

General

Toxicity due to capecitabine administration can be managed by symptomatic treatment and/or dose modification (treatment interruption or dose reduction). Once the dose is reduced, it should not be increased at any subsequent time. For toxicities thatthe physician considers unlikely to worsen or become life-threatening, such as alopecia, taste disturbances, or nail lesions, treatment may be continued at the same dose without reduction or interruption. Patients receiving capecitabine should be informed of the need to immediately discontinue treatment if moderate or severe toxicity occurs. Capecitabine doses not administered due to toxicity will not be replaced. Recommended dose modifications based on toxicity are listed below:

Table 3 Capecitabine dose reduction schedule (3-week cycle or continuous treatment)

Degrees of toxicity*	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose (% of initial dose)**
• *Grade 1*	Maintain the dose level	Maintain the dose level
• *Grade 2*		
-1st appearance	Discontinue until resolution to grade 0-1	100% 75% 50%
-2nd appearance	Discontinue treatment immediately permanent	Not applicable
-3rd appearance		
-4th appearance		
• *Grade 3*		
-1st appearance	Discontinue until resolution to grade 0-1	75% 50%
-2nd appearance	Discontinue treatment immediately permanent	Not applicable
-3rd appearance		
• *Grade 4*		
-1st appearance	Permanently interrupt	50%

either

If the doctor considers that it is morebeneficial for the patient to continue, Discontinue until resolution to grade 0-1	Not applicable

-2nd occurrence Discontinue permanently

*According to the Common Toxicity Criteria of the Clinical Trial Group of the National Cancer Institute of Canada (NCIC CTG) (version 1) or the US National Cancer Institute's Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. For hand-foot syndrome and hyperbilirubinemia,see section 4.4.

Hematology

Patients with a baseline neutrophil count < 1.5 x 109 /l and/or platelet count < 100 x 109 /l should not be treatedwith capecitabine. If any unscheduled laboratory test is performed during a treatment cycle and the neutrophil count falls below 1.0 x 109 /l or the platelet count falls below 75 x 109 /l, capecitabine should be discontinued.

Dose modifications for toxicity when using capecitabine in a 3-week cycle incombination with other medications

Dose modifications due to toxicity when using capecitabine in a 3-week cycle in combination with other drugs should be made according to Table 3 above for capecitabine and as indicated in its SmPC for the other drug(s).

If a delay in treatment is necessary at the start of a treatment cycle, either due to capecitabine or another drug(s),then the administration of the entire treatment should be delayed until the requirements for restarting all drugs are met.

If during the treatment cycle the doctor considers that these toxicities are not related to capecitabine, treatment with capecitabine should be continued and the dose of the other should be adjusted. medication according to its technical data sheet.

If treatment with the other medicine(s) has to be permanently discontinued,
You may resume treatment with capecitabine when the requirements for restarting the treatment are met.treatment with capecitabine.

This warning applies to all indications and all special populations.

Dose modifications due to toxicity when capecitabine is used continuously in combination with other drugs

Dose modifications for toxicity when capecitabine is used continuously in
Combination with other drugs should be carried out as indicated in Table 3 for capecitabine and accordingto the specifications for the other drug(s).

Dosage adjustments in special populations:

Liver failure
There are insufficient safety and efficacy data in patients with hepatic impairment to recommend a dose adjustment. No information is available regarding liver failure due to cirrhosis orhepatitis.

Kidney failure
Capecitabine is contraindicated in patients with severe renal impairment (baseline creatinine clearance below 30 ml/min [Cockcroft and Gault]). The incidence of grade 3 or 4 adverse reactions in patients withmoderate renal impairment (baseline creatinine clearance 30-50 ml/min) is increased compared to the general population. In patients with moderate baseline renal impairment, a reduced dose consisting of 75% of the initial dose of 1250 mg/m2 is recommended .

In patients with moderate baseline renal impairment, no dose reduction is necessary for a starting dose of 1000 mg/m2 . In patients with mild baseline renal impairment (baseline creatinine clearance 51-80 ml/min) no initial dose adjustment is required. Careful monitoring is recommended andprompt discontinuation of treatment is recommended if the patient develops a grade 2, 3 or 4 adverse reaction during treatment, with subsequent dose adjustments being specified in Table 3 above. If duringtreatment the calculated creatinine clearance falls below 30 ml/min, treatment with Capecitabine shouldbe discontinued. These dosage adjustment recommendations for renal impairment apply to both monotherapy and combination therapy (see also the following section “Elderly patients”).

Elderly patients
During treatment with capecitabine monotherapy, no adjustment of the initial dose is necessary. However, treatment-related grade 3 or 4 adverse reactions were more frequent in patients ÿÿ60 years ofage compared with younger patients.
When capecitabine was used in combination with other drugs, elderly patients (ÿ65 years) developedmore grade 3 and 4 adverse drug reactions, including those leading to treatment discontinuation, compared with younger patients. Careful monitoring of patients ÿ60 years is advised.

- *In combination with docetaxel:* a higher incidence of adverse reactions has been observed. Grade 3 or 4 treatment-related adverse reactions and serious treatment-related adverse reactionstreatment in patients aged 60 years or older (see section 5.1). For

patients aged 60 years or older,it is advisable to start treatment with a 75% dose reduction of capecitabine.
(950 mg/m2 twice daily). If no toxicity is observed in patients ÿÿ60 years treated with a reduced starting dose of capecitabine in combination with docetaxel, the starting doseCapecitabine could be cautiously increased to 1250 mg/m2 twice daily.

Pediatric population

There is no specific use recommendation for capecitabine in the pediatric population for indications for colon, colorectal, gastric and breast cancer. Recommended dosage (see section 5.1).

Monotherapy

Colon, colorectal and breast cancer The recommended starting dose of capecitabine when administered as monotherapy in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or locally advanced or metastatic breast cancer is 1,250 mg/m2 administered twicedaily (morning and evening; equivalent to a total daily dose of 2,500 mg/m2) for 14 days followed by a 7-day rest period. The recommended duration of adjuvant treatment in patients with stage III colon cancer is 6 months.

Combination treatment Colon, colorectal and gastric cancer In combination treatment, the recommended starting dose of capecitabine should be reduced to 800 – 1000 mg/m2 when administered twice daily for 14 days followed by a 7-day rest period, or to 625 mg/m2 twice daily when administered continuously (see section 5.1).
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Breast cancer In combination with docetaxel, the recommended starting dose of capecitabine for the treatment of metastatic breast cancer is 1,250 mg/m2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at a dose of 75 mg/m2 as an intravenous infusion, administered over 1 hour, every 3 weeks. According to the SmPC for docetaxel, premedication with an oral corticosteroid, such as dexamethasone, should be started before administering docetaxel to patients treated with the capecitabine plus docetaxel combination.

Capecitabine Normon dose calculation

Table 1 Calculation of standard and reduced dose based on body surface area for a starting dose of

capecitabine of 1250 mg/m2

	Dose level 1250 mg/m2 (twice daily)			
	Full dose	Number of 150 mg tablets and/or 500 mg tablets per administration (each dose must be administered in the morning and at night)	Reduced dose (75%)	Reduced dose (50%)
	1250 mg/m2		950 mg/m2	625 mg/m2
Body surface area (m2)	Dose per administration (mg)	150 mg 500 mg	Dose per administration (mg)	Dose per administration (mg)

ÿ1.26	1500	-	3	1150	800
1.27 - 1.38	1650	1	3	1300	800
1.39 - 1.52	1800	2	3	1450	950
1.53 - 1.66	2000	-	4	1500	1000
1.67 - 1.78	2150	1	4	1650	1000
1.79 - 1.92	2300	2	4	1800	1150
1.93 - 2.06	2500	-	5	1950	1300
2.07 - 2.18	2650	1	5	2000	1300
ÿ2.19	2800	2	5	2150	1450

Table 2 Calculation of the standard and reduced dose according to body surface area for an initial dose ofcapecitabine 1000 mg/m2

Dose level 1000 mg/m2 (twice daily)

Body surface area (m2)	Full dose			Reduced dose (75%)	Reduced dose (50%)
	1000 mg/m2	Number of tablets of 150 mg and/or tablets of 500 mg per administration (each take must be managed by the tomorrow and in the evening)		750 mg/m2	500 mg/m2
	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
ÿ1.26	1150	1	2	800	600
1.27 - 1.38	1300	2	2	1000	600
1.39 - 1.52	1450		2	1100	750
1.53 - 1.66	1600	3 4	2	1200	800
1.67 - 1.78	1750	5	2	1300	800
1.79 - 1.92	1800	2	3	1400	900
1.93 - 2.06	2000	-	4	1500	1000
2.07 - 2.18	2150	1	4	1600	1050
ÿ2.19	2300	2	4	1750	1100

Dosage adjustments during treatment:

General

Toxicity due to capecitabine administration can be managed by symptomatic treatment and/or dose modification (treatment interruption or dose reduction). Once the dose is reduced, it should not be increased at any subsequent time. For toxicities thatthe physician considers unlikely to worsen or become life-threatening, such as alopecia, taste disturbances, or nail lesions, treatment may be continued at the same dose without reduction or interruption. Patients receiving capecitabine should be informed of the need to immediately discontinue treatment if moderate or severe toxicity occurs. Capecitabine doses not administered due to toxicity will not be replaced. Recommended dose modifications based on toxicity are listed below:

Table 3 Capecitabine dose reduction schedule (3-week cycle or continuous treatment)

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• *Grade 2*		
-1st appearance	Discontinue until resolution to grade 0-1	100% 75% 50%
-2nd appearance	Discontinue treatment immediately permanent	Not applicable
-3rd appearance		
-4th appearance		
• *Grade 3*		
-1st appearance	Discontinue until resolution to grade 0-1	75% 50%
-2nd appearance	Discontinue treatment immediately permanent	Not applicable
-3rd appearance		
• *Grade 4*		
-1st appearance	Permanently interrupt	50%

	either	
	If the doctor considers that it is morebeneficial for the patient to continue, Discontinue until resolution to grade 0-1	Not applicable
	-2nd occurrence Discontinue permanently	

*According to the Common Toxicity Criteria of the Clinical Trial Group of the National Cancer Institute of Canada (NCIC CTG) (version 1) or the US National Cancer Institute's Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. For hand-foot syndrome and hyperbilirubinemia,see section 4.4.

Hematology

Patients with a baseline neutrophil count < 1.5 x 109 /l and/or platelet count < 100 x 109 /l should not be treated withcapecitabine. If any unscheduled laboratory test is performed during a treatment cycle and the neutrophil count falls below 1.0 x 109 /l or the platelet count falls below 75 x 109 /l, capecitabine should be discontinued.

Dose modifications for toxicity when using capecitabine in a 3-week cycle incombination with other medications

Dose modifications due to toxicity when using capecitabine in a 3-week cycle in combination with other drugsshould be made according to Table 3 above for capecitabine and as indicated in its SmPC for the other drug(s).

If a delay in treatment is necessary at the start of a treatment cycle, either due to capecitabine or another drug(s), then the administration of the entire treatment should be delayed until the requirements for restarting all drugs aremet.

If during the treatment cycle the doctor considers that these toxicities are not related to capecitabine, treatment with capecitabine should be continued and the dose of the other drug should be adjusted.
medication according to its technical data sheet.

If treatment with the other medicine(s) has to be permanently discontinued,
You may resume treatment with capecitabine when the requirements for restarting the treatment are met.
treatment with capecitabine.

This warning applies to all indications and all special populations.

Dose modifications due to toxicity when capecitabine is used continuously in combination with other drugs

Dose modifications for toxicity when capecitabine is used continuously in
Combination with other drugs should be carried out as indicated in Table 3 for capecitabine and according to the specifications for the other drug(s).

Dosage adjustments in special populations:

Liver failure
There are insufficient safety and efficacy data in patients with hepatic impairment to recommend a dose adjustment. No information is available regarding liver failure due to cirrhosis orhepatitis.

Kidney failure
Capecitabine is contraindicated in patients with severe renal impairment (baseline creatinine clearance below 30 ml/min [Cockcroft and Gault]). The incidence of grade 3 or 4 adverse reactions in patients withmoderate renal impairment (baseline creatinine clearance 30-50 ml/min) is increased compared to the general population. In patients with moderate baseline renal impairment, a reduced dose consisting of 75% of the initial dose of 1250 mg/m2 is recommended .

In patients with moderate baseline renal impairment, no dose reduction is necessary for a starting dose of 1000 mg/m2 . In patients with mild baseline renal impairment (baseline creatinine clearance 51-80 ml/min) no initial dose adjustment is required. Careful monitoring is recommended andprompt discontinuation of treatment is recommended if the patient develops a grade 2, 3 or 4 adverse reaction during treatment, with subsequent dose adjustments being specified in Table 3 above. If duringtreatment the calculated creatinine clearance falls below 30 ml/min, treatment with Capecitabine shouldbe discontinued. These dosage adjustment recommendations for renal impairment apply to both monotherapy and combination therapy (see also the following section “Elderly patients”).

Elderly patients
During treatment with capecitabine monotherapy, no adjustment of the initial dose is necessary. However, treatment-related grade 3 or 4 adverse reactions were more frequent in patients ÿÿ60 years ofage compared with younger patients.
When capecitabine was used in combination with other drugs, elderly patients (ÿ65 years) developedmore grade 3 and 4 adverse drug reactions, including those leading to treatment discontinuation, compared with younger patients. Careful monitoring of patients ÿ60 years is advised.

- *In combination with docetaxel:* a higher incidence of adverse reactions has been observed. Grade 3 or 4 treatment-related adverse reactions and serious treatment-related

adverse reactionstreatment in patients aged 60 years or older (see section 5.1). For patients aged 60 years or older,it is advisable to start treatment with a 75% dose reduction of capecitabine.
(950 mg/m2 twice daily). If no toxicity is observed in patients ÿÿ60 years treated with a reduced starting dose of capecitabine in combination with docetaxel, the starting doseCapecitabine could be cautiously increased to 1250 mg/m2 twice daily.

Pediatric population
There is no specific use recommendation for capecitabine in the pediatric population forindications for colon, colorectal, gastric and breast cancer.

Method of administration

Oral route.

Capecitabine Normon tablets should be swallowed whole with water within 30 minutes after a meal.

The tablets should not be crushed or divided.

4.3. Contraindications

- History of severe and unexpected reactions to treatment with fluoropyrimidines,
- Hypersensitivity to capecitabine, to any of the excipients listed in section 6.1 or tofluorouracil,
- Known complete deficiency of dihydropyrimidine dehydrogenase (DPD) activity (see section 4.4),
- During pregnancy and breastfeeding,
- In patients with severe leukopenia, neutropenia or thrombocytopenia,
- In patients with severe hepatic impairment,
- In patients with severe renal impairment (creatinine clearance below 30 ml/min),
- Recent or concomitant treatment with brivudine (see section 4.4 and 4.5 for drug interactions),
- If there are contraindications to any of the drugs in the combination regimen, do not you should use that medicine.

4.4. Special warnings and precautions for use

Dose-limiting toxic effects

Dose-limiting toxic effects include diarrhea, abdominal pain, nausea, stomatitis, and hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia). Most of the Adverse reactions are reversible and do not require permanent discontinuation of treatment, althoughDosage may need to be discontinued or reduced.

Diarrhea

Patients with severe diarrhea should be carefully monitored and given fluids and electrolyte replacement if theybecome dehydrated. Standard antidiarrheal treatments (e.g., loperamide) may be used. NCIC CTC defines grade 2 diarrhea as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an increase of ÿÿ10 stools/day or melena or the need for parenteral support. The dose reduction will be carried outas needed (see section 4.2).

Dehydration

Dehydration should be prevented or corrected from the outset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may become dehydrated more rapidly. Dehydration may cause acute renal failure, especially in patients with pre-existing renal impairment or when capecitabine is given concomitantly with otherknown nephrotoxic medicinal products. Acute renal failure secondary to dehydration may be life-threatening. If Grade 2 (or greater) dehydration occurs, capecitabine should be discontinued immediately and the dehydrationcorrected. Treatment should not be restarted until the patient has been

rehydrated and the precipitating causeshave been corrected or controlled. Dose modifications should be made as necessary based on the precipitatingadverse reaction (see section 4.2).

Hand-foot syndrome
Hand-foot syndrome also known as hand-foot skin reaction, palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema. Grade 1 hand-foot syndrome is defined as
Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/orfeet and/or discomfort that does not alter the patient's normal activities.

Grade 2 hand-foot syndrome is defined as painful erythema and swelling of the hands and/or feet, causing discomfort that affects the patient's daily activities. Grade 3 hand-foot syndrome is defined as moist desquamation, ulceration, appearance of blistering and severe pain in the hands and/or feet and/or severe discomfort causing the patient to be unable to work or perform activities of daily living. Persistent or severe hand-foot syndrome (Grade 2 and above) may lead to loss of fingerprints over time, which may affect patient identification. If Grade 2 or 3 hand-foot syndrome occurs, capecitabine should be discontinued until the condition resolves or decreases in intensity to Grade 1.

After grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased. When capecitabine and cisplatin are used in combination, the use of vitamin B6 (pyridoxine) for secondary or symptomatic prophylactic treatment of hand-foot syndrome is not recommended, as there are published reports that its use may decrease the efficacy of cisplatin. In patients treated with capecitabine, there is some evidence that dexpanthenol is effective in the prophylaxis of hand-foot syndrome.

Cardiotoxicity

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiogram changes (including very rare cases of QT prolongation). These adverse reactions were more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias (including ventricular fibrillation, torsade de pointes and bradycardia), angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients treated with capecitabine. Caution should be exercised in patients with a history of significant cardiac disease, arrhythmias and angina pectoris (see section 4.8).

Hypo- or hypercalcemia

Hypo- and hypercalcaemia have been observed during treatment with capecitabine. Caution should be exercised in patients with pre-existing hypo- or hypercalcaemia (see section 4.8).

Disease of the central or peripheral nervous system

Caution should be exercised in patients with central or peripheral nervous system disease, e.g. brain metastases or neuropathy (see section 4.8).

Diabetes mellitus or electrolyte disturbances

Caution should be exercised in patients with diabetes mellitus or electrolyte disturbances as these may be aggravated during treatment with capecitabine.

Anticoagulation with coumarin derivatives
In a single-dose interaction study with warfarin, a significant increase in mean AUC (+57%) of S-warfarin was observed. Theseresults suggest an interaction, probably due to an inhibition by capecitabine of the cytochrome P450 2C9 isoenzyme system.

Patients receiving concomitant therapy with capecitabine and oral coumarin-derived anticoagulants should have their anticoagulant response (INR or prothrombin time) closely monitored and the anticoagulant dose adjusted accordingly (seesection 4.5).

Brivudine
Brivudine must not be administered concomitantly with capecitabine. Fatal cases have been reported following this druginteraction. There should be at least a 4-week waiting period between the end of treatment with brivudine and the start of therapy with capecitabine. Treatment with brivudine should be started 24 hours after the last dose of capecitabine (see sections 4.3 and 4.5). In the event of accidental administration of brivudine to patients being treated with capecitabine, effective measures should be taken to reduce the toxicity of capecitabine.

It is recommended to go to the hospital immediately. All measures to prevent systemic infections and dehydration should beinitiated.

Liver failure

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 hepatic impairment, regardless ofwhether liver metastases are present. Capecitabine should be discontinued if treatment-related increases in bilirubin >3.0 x ULN or hepatic aminotransferases (ALT, AST) >2.5 x ULN occur.
Capecitabine monotherapy may be resumed if bilirubin decreases to ÿ3.0 x ULN or hepaticaminotransferases decrease to ÿ2.5 x ULN.

Kidney failure

The incidence of grade 3 or 4 adverse reactions is increased in patients with moderate renal impairment(creatinine clearance 30-50 ml/min) compared to the normal population (see sections 4.2 and 4.3).

Dihydropyrimidine dehydrogenase (DPD) deficiency

DPD activity determines the rate of 5-fluorouracil catabolism (see section 5.2). Patients with DPD deficiency are therefore atincreased risk of fluoropyrimidine-related toxicity, including, for example, stomatitis, diarrhoea, mucositis, neutropenia and neurotoxicity.

Toxicity related to DPD deficiency usually occurs during the first treatment cycle or after increasing thedose.

Complete DPD deficiency

Complete DPD deficiency is rare (0.01%-0.5% of the Caucasian population). Patients with complete DPD deficiency are at increased risk of life-threatening or fatal reactions and should not be treated withCapecitabine Normon (see section 4.3).

Partial DPD deficiency

Partial DPD deficiency is estimated to affect 3-9% of the Caucasian population. Patients with partialDPD deficiency are at increased risk of severe and potentially fatal toxicity. A reduced starting doseshould be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be considered along with other routine measures for dose reduction. Reduction of the initial dose may affect the efficacy of treatment. In the absence of severe toxicity, subsequent doses may be increasedunder close monitoring.

DPD deficiency test

Phenotypic and/or genotypic testing is recommended prior to initiation of treatment with Capecitabine Normon, despite uncertainty regarding optimal pretreatment testing methodologies. Applicable clinical guidelines should be considered.

Genotypic characterization of DPD deficiency

Testing for rare mutations in the DPYD gene before treatment may help identify patients with DPDdeficiency.

The four DPYD gene variants c.1905+1G>A [also known as DPYD*2aA], c.1679T>G [DPYD*13], c.2846A>T, and c.1236G>A/HapB3, can result in a complete absence or reduced DPD enzyme activity. Other rare variants may also be associated with an increased risk of serious or life-threateningtoxicity.

Certain homozygous mutations and compound heterozygous mutations at the DPYD gene locus (e.g., combinations of all fourvariants with at least one allele of c.1905+1G>A or c.1679T>G) are known to result in complete or near-complete absence of DPD enzymatic activity.

Patients with certain heterozygous DPYD variants (including c.1905+1G>A, c.1679T>G, c. 2846A>T, andc.1236G>A/HapB3 variants) are at increased risk for severe toxicity when treated with fluoropyrimidines.

The frequency of the heterozygous genotype c.1905+1G>A in the DPYD gene in Caucasian patients isaround 1%, 1.1% for the c.2846A>T variants, 2.6-6.3% for c.1236G>A/HapB3 and 0.07% to 0.1% for c.1679T>G.

Data on the frequency of the four DPYD gene variants in populations other than Caucasians are limited. Atpresent, all four DPYD variants (c.1905+1G>A, c.1679T>G, c.2846A>T, and c.1236G>A/HapB3) are considered to be virtually absent in populations of African-American or Asian origin.

Phenotypic characterization of DPD deficiency

For phenotypic characterization of DPD deficiency, pretreatment measurement of plasma levels of uracil(U), the endogenous substrate of DPD, is recommended.

Elevated pretreatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainty about the uracil thresholds defining complete and partial DPD deficiency, a blood uracil levelÿ16 ng/mL and ÿ150 ng/mL should be considered indicative of partial DPD deficiency and associated withan increased risk of fluoropyrimidine toxicity. A blood uracil level ÿ150 ng/mL should be considered indicative of complete DPD deficiency and associated with an increased risk of life-threatening or fatal fluoropyrimidine toxicity.

Ophthalmological complications

Patients should be carefully monitored for ophthalmologic complications, such as ~~keratitis and corneal~~ disorders, particularly if they have a history of ocular disorders. Treatment for ocular disorders should beinitiated when clinically appropriate.

Severe skin reactions

~~Capecitabine may induc~~e severe skin reactions such as Stevens-Johnson syndrome and toxic epidermalnecrolysis. Treatment with Capecitabine Normon should be discontinued in patients with
patients who experience a severe skin reaction during treatment.

Warning on excipients:
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactasedeficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially'sodium-free'.

~~Capecitabine Normon tablets~~ must not be crushed or divided. Exposure of either the patient or the caregiverto crushed or divided Capecitabine Normon tablets may result in related adverse reactions (see section 4.8).

4.5. Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Interaction with other medications

Brivudine

A clinically significant interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-Fluorouracil,tegafur) has been reported, resulting from the inhibition of dihydropyrimidine dehydrogenase by brivudine. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Brivudine should therefore not be administered with capecitabine (see section

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4.3 and 4.4). There should be at least a 4-week waiting period between the end of treatment with brivudine andthe start of therapy with capecitabine. Treatment with brivudine may be started 24 hours after the last dose of capecitabine.

Substrates of cytochrome P-450 2C9

Apart from warfarin, no formal interaction studies have been performed between capecitabine and other CYP2C9substrates. Special caution should be exercised when co-administering capecitabine and CYP2C9 substrate (e.g. phenytoin). See also interactions with anticoagulants and coumarin derivatives below, and section 4.4.

Coumarin-derived anticoagulants

Abnormal coagulation parameters and/or bleeding have been observed in patients treated with capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin or phenprocoumon. These reactions occurwithin a few days to several months after starting capecitabine therapy and, in a few cases, within the first monthafter stopping capecitabine therapy.

In a pharmacokinetic interaction study using a single 20 mg dose of warfarin, treatment with capecitabine increased the AUC of S-warfarin by 57% and the INR by 91%. Since the metabolism of R-warfarin was not affected, these results indicate that capecitabine inhibits the 2C9 isoenzyme but has no effect on the 1A2 and3A4 isoenzymes. Patients taking coumarin-derived anticoagulants concomitantly with capecitabine should be regularly monitored for alterations in coagulation parameters (PT or INR) and the anticoagulant dose should beadjusted accordingly.

Phenytoin

An increase in phenytoin plasma concentrations, which in isolated cases has led to symptoms of phenytoin toxicity, has been observed during concomitant use of capecitabine with phenytoin. Patients taking phenytoinconcomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Folinic acid/ folic acid

A combination study of capecitabine and folinic acid (leucovorin) showed that folinic acid had no major effect onthe pharmacokinetics of capecitabine and its metabolites. However, folinic acid has an effect on the pharmacodynamics of capecitabine and its toxicity may be increased by folinic acid: the maximum tolerated dose (MTD) of capecitabine monotherapy using the intermittent regimen is 3000 mg/m2 per day whereas it is only 2000 mg/m2 per day when capecitabine is combined with folinic acid.

(30 mg twice daily orally). Increased toxicity may be relevant when switching from

5-FU/LV to a capecitabine regimen. This may also be relevant with folic acid supplementation for folic acid deficiency, due to the similaritybetween folinic acid and folic acid.

Antacid

The effect of an antacid containing aluminium hydroxide and magnesium hydroxide on the pharmacokinetics ofcapecitabine was studied. There was a small increase in the plasma concentrations of capecitabine and one metabolite (5'-DFCR); there was no effect on the 3 major metabolites (5'-DFUR, 5-FU and FBAL).

Allopurinol

Interactions of 5-FU with allopurinol have been observed, which may decrease the efficacy of 5-FU. Concomitantuse of allopurinol with capecitabine should be avoided.

Interferon alpha

When combined with interferon alfa-2a (3 MIU/m2 per day), the MTD of capecitabine was 2000 mg/m2 per daywhereas it was 3000 mg/m2 per day when capecitabine was used alone.

Radiotherapy

The maximum tolerated dose (MTD) of capecitabine monotherapy using the intermittent regimen is 3000 mg/m2 whereas, whencombined with radiotherapy for rectal cancer, the MTD of capecitabine is 2000 mg/m2 per day regardless of whether a continuous treatment regimen is followed or whether it is administered daily Monday through Friday for a 6-day radiotherapy cycle.
weeks.

Oxaliplatin

When capecitabine was administered in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab, therewere no clinically significant differences in exposure to capecitabine or its metabolites, free platinum, or total platinum.

Bevacizumab

Bevacizumab in the presence of oxaliplatin did not produce any clinically significant effect on the pharmacokinetic parametersof capecitabine or its metabolites.

Interaction with food

In all clinical trials, patients were instructed to take capecitabine within 30 minutes after a meal. As current safety and efficacy data are based on administration with food, it is recommended that capecitabine be administered with food. Administration with food decreases the rate of absorption of capecitabine (see section 5.2).

4.6. Fertility, pregnancy and lactation

Women of childbearing age / Contraception in men and women

Women of childbearing potential should be advised to avoid pregnancy while being treated with capecitabine. If the patient becomes pregnant during treatment with capecitabine, this should be
informed of the potential risk to the fetus. Effective contraception should be used during treatment and for 6 months after the lastdose of capecitabine.

Based on findings of genetic toxicity, male patients with female partners of reproductive potential should use effectivecontraception during treatment and for 3 months after the last dose of capecitabine.

Pregnancy

There are no studies on capecitabine in pregnant women, however, it must be admitted that capecitabinemay cause fetal harm when administered to a pregnant woman. Capecitabine administration producedembryonic mortality and teratogenicity in reproductive

toxicity studies in animals. These data constitute expected effects of fluoropyrimidine derivatives. Capecitabine iscontraindicated during pregnancy.

Lactation

It is not known whether capecitabine is excreted in human milk. No studies have been conducted to evaluate the impact of capecitabine on milk production or its presence in human milk. In lactating mice, significant amounts of capecitabine and itsmetabolites have been detected in the milk. Because the potential harm to the nursing infant is unknown, breast-feeding should be discontinued while receiving capecitabine and for 2 weeks after the final dose.

Fertility

There are no data on capecitabine and its impact on fertility. In the pivotal studies of capecitabine, Women of childbearing potential and men were included only if they agreed to use an acceptable method of birth control to preventpregnancy during the study and for a reasonable period after it ended.

Effects on fertility have been observed in animal studies (see section 5.3).

4.7. Effects on ability to drive and use machines

Capecitabine has minor or moderate influence on the ability to drive and use machines. Capecitabine may cause dizziness, fatigue and nausea.

4.8. Adverse reactions

Summary of the safety profile

The overall safety profile of capecitabine is based on data from more than 3000 patients treated with capecitabine monotherapy or capecitabine in combination with different chemotherapy regimens acrossmultiple indications. The safety profiles of capecitabine monotherapy are comparable in the metastaticbreast cancer, metastatic colorectal cancer and adjuvant colon cancer populations.
Section 5.1 details the main trials conducted, including their design and main efficacy results.

The most frequently reported and/or clinically relevant treatment-related adverse reactions (ADRs) weregastrointestinal disorders (especially diarrhea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-plantar erythrodysesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal failure in patients with pre-existing compromised renal function, and thrombosis/embolism.

Table of adverse reactions

Adverse reactions considered by the investigator to be possibly, probably or remotely related to the administration of capecitabine are listed in Table 4 for capecitabine administered as monotherapy and
in Table 5 for capecitabine administered in combination with different chemotherapy regimens in multipleindications. The following categories are used to classify ADRs by frequency: very common (ÿ1/10), common (ÿ1/100 to < 1/10), uncommon (ÿ1/1,000 to < 1/100), rare (ÿ1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Capecitabine monotherapy

Table 4 lists ADRs associated with the use of capecitabine monotherapy based on a pooled analysis ofsafety data from the three pivotal clinical trials involving over 1900 patients (studies M66001, SO14695,and SO14796). ADRs are aggregated into the appropriate frequency group based on the overall incidence obtained from the pooled analysis.

Table 4 Summary of ADRs reported in patients treated with capecitabine monotherapy

System of classification of	**organs**	**Very common (ÿ1/10)**		*All grades*
		All grades	**Frequently Asked Questions**	
			(ÿ 1/100 to < 1/10)	

Uncommon (ÿ 1/1,000 to < 1/100) *Serious and/ or life-threatening (grade 3-4) or considered medically relevant*	**Rare / Very rare (ÿ 1/10,000 to < 1/1,**	**000) (Post-marketing experience)**

Infections and infestations	---	Herpes infection, Nasopharyngitis, Tract infection lower respiratory	Sepsis, Urinary tract infection, Cellulitis, Tonsillitis, Pharyngitis, Oral candidiasis, Flu, Gastroenteritis, Fungal infection, Infection, Dental abscesses
Benign, malignant and unspecified neoplasms	---	---	Lipoma
Disorders of the blood and lymphatic system	---	Neutropenia, Anemia	Febrile neutropenia, Pancytopenia, Granulocytopenia, Thrombocytopenia,

	y	s	ers	
	c	syste	vascul	
	h	m	ar	
	i			
	a			---
Diso	t	Eye disorders	Disorders	
rder	r		respiratory,	
s of	i		thoracic	Anorexia
the	c		and	
syst			mediasti	
em			nal	
imm	D	Ear disorders		---
unol	i	and the labyrinth		
ogic	s	D		
al	o	is		---
Diso	r	o		
rder	d	r		
s of	e	d		
the	r	er		
metabolis m and nutrition	s	s		---
		c		
	o	ar		
D	f	di		
i		a		---
s	t	c		
o	h			---
r	e			
d				
e	n	D		
r	e	is		
s	r	o		---
p	v	r		
s	o	d		
	u			

---		somnia, Depression	Leukopenia, Hemolytic anemia, Increased	Vertigo, Earache
	- - -	Headache, Lethargy, Vertigo, Paresthesia, Dysgeusia	normalized index international normalized ratio (INR)/ Prolonged prothrombin time	Unstable angina, Angina pectoris, Myocardial ischemia/ infarction, Atrial fibrillation, Arrhythmia, Tachycardia, Sinus tachycardia, Palpitations Vein thrombosis deep, Hypertension, Petechiae, Hypotension, Flushing with a sensation of heat, Peripheral cold sensation Pulmonary embolism, Pneumothorax, Hemoptysis, Asthma, Dyspnea on exertion
	D e h y d r a t i o n , W e i g h t l o s s	Increase in tearing, Conjunct ivitis, Eye irritation --- --- Thrombophle bitis Dyspnea, Epistaxis, Cough, Rhinorrhea	Hypersensitivity Diabetes, Hypokalemia, Appetite disturbance, Malnutrition, Hypertriglyceri demia, Confusional state, Panic attacks, Depressed mood, Decreased libido Aphasia, Memory impairment, Ataxia, Syncope, Balance disorder, Sensory disorders, Peripheral neuropathy Decreased visual acuity, Diplopia	
	I n			

	c l e u k o e n c e p h a l o	pathy (very rare)		, keratitis (rare), punctate keratitis (rare)	
Angioedema		Duct stenosis lacri mal (rare) , corne al abnor malit y (rare)		Ventricular fibrillation (rare), QT prolongati on (rare), Torsade de pointes (rare), bradycard ia (rare), vasospas m (rare)	
Toxi					
	Dis ord ers gast roin testi nal	*pato bilia ry*	Diarrhe a, Vomitin g, Nausea, Stomatitis, Abdominal pain	Gastrointestinal hemorrhage, Constipation, Upper abdominal pain, Dyspepsia, Flatulence, Dry mouth	Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Pain in the lower abdominal tract, Esophagitis, Abdominal discomfort, Gastroesophageal reflux disease, Colitis, blood in stool Jaundice
			---	Hyperbilirubinemi a, Changes in the liver function tests	
	Di so rd er s he				

	e	i	re	patitis
	p	l	),	(rare)
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Disorders of the skin and subcutaneous tissue	Syndrome erythrodysesthesia palmo-plantar**	Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyperpigmentation, Macular rash, Skin peeling, Dermatitis,	Blisters, Skin ulcers, Rash, Hives, Photosensitivity reaction, Palmar erythema, Facial swelling, Purpura, Radiation hypersensitivity syndrome.	Cutaneous lupus erythematosus (rare), severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare) (see section 4.4)
	---	Alteration of the pigmentation,		
Disorders muscuoskeletal and connective tissue	---	Nail alteration Pain in the extremities, Back pain, Arthralgia	Joint swelling, Bone pain, Facial pain, Musculoskeletal stiffness, Muscle weakness	
Kidney and urinary disorders		---	Hydronephrosis, Urinary incontinence, Hematuria, Nocturia, Increased blood creatinine	
Disorders of the reproductive and breast system	*Disorder*	*s*	*and administration site conditions*	
		General		

---	---	ture Vaginal bleeding
Fatigue, Asthenia	Pyrexia, Peripheral edema, Malaise, Chest pain	Edema, Chills, Flu symptoms, Stiffness, Increased body tempera

** Based on post-marketing experience, persistent or severe palmar-plantar erythrodysesthesiasyndrome may lead to loss of fingerprints over time (see section 4.4).

Capecitabine in combination therapy:

Table 5 lists ADRs associated with the use of capecitabine in combination with different chemotherapyregimens in multiple indications based on safety data from over 3000 patients. ADRs have been addedin the appropriate frequency group (Very common or Common) based on the high incidence observedin any of the pivotal clinical trials and which differ from those observed with capecitabine monotherapyor have been observed with a higher frequency compared to capecitabine monotherapy (see Table 4).Uncommon ADRs reported with capecitabine combination therapy are consistent with ADRs reported with capecitabine in monotherapy or reported with capecitabine monotherapy in addition to the combination drug (in theliterature and/or in the corresponding SmPC).

Some of the ADRs are reactions frequently observed with the combination drug (e.g. sensory peripheralneuropathy with docetaxel or oxaliplatin, hypertension with bevacizumab); however, an aggravation with capecitabine therapy cannot be excluded.

Table 5 Summary of ADRs reported in patients treated with capecitabine in combination that differ fromthose observed with capecitabine monotherapy or that have been observed with a higher frequency compared to capecitabine monotherapy

Classification system of organs	**Very frequent** *All degrees* ---	**Frequently Asked Questions**	**Rare/Very rare (Post-marketing experience**
Infections and infestations		*All grades* Shingles, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection, Rhinitis, Flu, +Infection, Oral Herpes	
Blood and lymphatic system disorders	*gical Metabolism disorders and nutrition*	*disorders highly strung*	
System disorders immunolo	*Psychiatric disorders System*	*Eye disorders Ear and labyrinth disorders Heart disorders*	

Vascular disorders	+Neutropenia, +Leukopenia, +Anemia, +Neutropenic fever, Thrombocytopenia	Bone marrow depression, +Febrile neutropenia
	---	Hypersensitivity
	Decreased appetite	Hypokalemia, Hyponatremia, Hypomagnesemia, Hypocalcemia, Hyperglycemia
	---	Sleep disturbances, Anxiety
	Paresthesia, Dysesthesia, Peripheral neuropathy, Sensory peripheral neuropathy, Dysgeusia, Headache	Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoesthesia
	Increased tearing	

	Edema of the lower extremities, Hypertension, +Embolism and thrombosis	Visual disorders, Dry eye, Eye pain, Visual disturbance, Blurred vision Ringing

i n t h e e a r s , H e a r i	n g l o s s A t r i a l f i b r i l l	ation, Cardiac ischemia/ infarction Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis

Respiratory, thoracic and mediastinal disorders	Sore throat, Pharyngeal dysesthesia	Hiccups, Pharyngolaryngeal pain, Dysphonia
Disorders gastrointestinal	Constipation, Dyspepsia	Upper gastrointestinal bleeding, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal reflux disease, Mouth pain, Dysphagia, Rectal bleeding, Lower abdominal pain, Oral dysesthesia, Oral paresthesia, Oral hypoesthesia, Abdominal discomfort
Hepatobiliary disorders	---	Altered liver function
Skin and subcutaneous tissue disorders	*Disorders musculoskeletal and connective tissue*	*Kidney disorders and urinals*
		General disorders and administration site conditions

Alopecia, nail disorder	Hyperhidrosis, Erythematous rash, Urticaria, Night sweats	site pain	
Myalgia, Arthralgia, Pain in extremities	Pain in the jaw, Muscle spasms, Lockjaw, muscle weakness		
---			Acute renal failure secondary to dehydration (strange)
Pyrexia, Weakness, +Lethargy, Temperature intolerance	Hematuria, Proteinuria, Decreased clearance renal creatinine, Dysuria Inflammation of the mucosa, Pain in the extremities, Pain, Chills, Chest pain, Flu symptoms, +Fever, Infusion-related reactions, Injection site reaction, Infusion site pain, Injection		

Traumatic injuries, poisoning and complications of therapeutic procedures		Contusion	

+ All grades were taken into account for the calculation of the frequency of each ADR. For terms marked with"+", the frequency calculation was based on grade 3-4 ADRs. ADRs have been added based on the high incidence observed in any of the main combination trials.

Description of relevant adverse reactions

Hand-foot syndrome (see section 4.4)

For the capecitabine dose of 1250 mg/m2 administered twice daily on days 1 to 14 of every 3 weeks, the frequencyof all-grade hand-foot syndrome was 53% to 60% in capecitabine monotherapy trials (including studies for adjuvanttreatment of colon cancer, treatment of metastatic colorectal cancer, and treatment of breast cancer) and 63% in a capecitabine/docetaxel arm for the treatment of metastatic breast cancer. For the capecitabine dose of 1000 mg/ m2 administered twice daily on days 1 to 14 of every 3 weeks in combination therapy with capecitabine, the frequency of all-grade hand-foot syndrome was 22% to 30%.

In a meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabine monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications (colon, colorectal, gastricand breast cancer) hand-foot syndrome (all grades) was observed to occur in 2066 patients (43%) after a median time of 239 days after initiation of capecitabine treatment [95% CI: 201 - 288]. Across all studies combined, the following covariates associated with an increased risk of developing hand-foot syndrome were statistically significant: increasing starting capecitabine dose (grams), decreasing cumulative capecitabine dose (0.1* kg), increasing relative dose intensity in the first six weeks, increasing duration of study treatment (weeks), increasingage (10-year increments), female sex, and good ECOG performance status (0 versus ÿ1).

Diarrhoea (see section 4.4)

Capecitabine may induce the onset of diarrhea, this has been observed in more than 50% of patients. Results from a meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabine showedthat across all studies combined, the following covariates associated with an increased risk of developing diarrhea were statistically significant: increasing starting capecitabine dose (grams), increasing duration of study treatment (weeks), increasing age (10-year increments), and female sex. The following covariates associated with a decreased risk of developing diarrhea were statistically significant: increasing cumulative capecitabine dose (0.1*kg) and increasing relative dose intensity in the first six months of treatment.

weeks.

Cardiotoxicity (see section 4.4)

In addition to the ADRs described in Tables 4 and 5, and based on a combined analysis of safety data from 7 clinical trials involving 949 patients (2 phase III trials and 5 phase II trials in metastatic colorectal cancer and metastatic breast cancer), the following

ADRs were associated with the use of capecitabine monotherapy with anincidence of less than 0.1%: cardiomyopathy, heart failure, sudden death, and ventricular extrasystoles.

Encephalopathy
In addition to the ADRs described in Tables 4 and 5, and based on the combined analysis of safety data from 7 clinical trials described above, encephalopathy was associated with the use of capecitabine monotherapy with anincidence of less than 0.1%.

Exposure to crushed or divided capecitabine tablets:
In case of exposure to crushed or divided capecitabine tablets, the following adverse reactions have been reported:eye irritation, eye inflammation, skin rash, headache, paresthesia, diarrhea, nausea, gastric irritation and vomiting.

Special populations

Elderly patients (see section 4.2)
Analysis of safety data among patients ÿ60 years of age treated with capecitabine monotherapy and an analysis of patients treated with the capecitabine plus docetaxel combination showed a higher incidence of treatment-related grade 3 and 4 adverse reactions and treatment-related serious adverse reactions compared with patients younger than 60 years of age. Patients ÿ60 years of age treated with capecitabine plus docetaxelalso had more premature treatment withdrawals due to adverse reactions compared with patients <60 yearsof age.

The results of a meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabineshowed that in all studies combined, the association of increasing age
(10-year increments) with an increase in the risk of developing hand-foot syndrome and diarrhea and with adecrease in the risk of developing neutropenia, was statistically significant.

Sex
The results of a meta-analysis of 14 clinical trials with data from over 4700 patients treated with capecitabine showed that in all studies combined, the association of female sex with an increased risk of developing hand-foot syndrome and diarrhea and with a decreased risk of developing neutropenia was statistically significant.

Patients with renal impairment (see sections 4.2, 4.4 and 5.2)
Analysis of safety data in patients with baseline renal impairment treated with capecitabine monotherapy (colorectal cancer) showedan increased incidence of treatment-related grade 3 and 4 adverse reactions compared to patients with normal renal function (36% in patients without renal impairment n=268, versus 41% in mild n=257 and 54% in moderate n=59, respectively) (see section 5.2). Patients with moderately impaired renal function showed an increased dose reduction (44%) versus 33% and 32% in patients with no or mild renal impairment and an increased rate of early discontinuation from treatment (21% withdrawals during the first two cycles) versus 5% and 8% in patients with no or mild renal impairment.

Reporting suspected adverse reactions: Reporting
suspected adverse reactions to the medicinal product after authorisation is important. This allows continuedmonitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to reportany suspected adverse reactions via the Spanish Pharmacovigilance System for Medicinal Products for Human Use: www.notificaram.es.

4.9. Overdose

Manifestations of acute overdose include nausea, vomiting, diarrhea, mucositis, irritation gastrointestinal and bleeding, as well as bone marrow depression. Medical management of overdose shouldinclude individualized therapy and supportive medical intervention aimed at correcting the manifestations clinics and prevent possible complications.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: cytostatic (antimetabolite). ATC code: L01BC06.

Mechanism of action

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate that, when administered orally, acts as a precursorto the cytotoxic 5-fluorouracil (5-FU). Capecitabine is activated through several enzymatic steps (see section5.2). The enzyme responsible for the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found
in tumor tissues as well as in normal tissues although at elevated levels.

generally lower. In human cancer xenograft models, capecitabine showed a synergistic effect incombination with docetaxel which may be related to the stimulation (upregulation) of thymidine phosphorylase produced by docetaxel.

There is evidence that the metabolism of 5-FU by anabolic pathway blocks the methylation reaction ofdeoxyuridylic acid to thymidylic acid, thereby interfering with 5-FU synthesis. deoxyribonucleic acid (DNA). The addition of 5-FU also leads to inhibition of RNA and protein synthesis.Since both DNA and RNA are essential for cell division and growth, the effect of 5-FU may create a thymidine deficiency that leads to unbalanced growth and cell death. The effects of DNA and RNA deprivation are accentuated in cells that proliferate more rapidly and that metabolize 5-FU more rapidly.

Colon and colorectal cancer:

Adjuvant therapy with capecitabine monotherapy in colon cancer

Data from a multicenter, randomized, controlled, phase III clinical trial (trial XACT; M66001) in patients with stage III colon cancer (Dukes stage C) support the use of capecitabinefor the adjuvant treatment of patients with colon cancer. In this trial, 1987 patients were randomized toreceive capecitabine (1250 mg/m2 twice daily for 2 weeks on followed by 1 week off, given in 3-week cycles for 24 weeks) or 5-FU and leucovorin (Mayo Clinic regimen: 20 mg/m2 leucovorin IV followed
by 425 mg/m2 5 -FU).
Intravenous bolus FU on days 1-5, every 28 days for 24 weeks). Capecitabine was at least equivalent to intravenous 5-FU/LV for disease-free survival in the protocol-enrolled population (hazard ratio 0.92; 95% CI 0.80-1.06). In the entire randomized population, tests to differentiate disease-free survival and overall survival for capecitabine versus 5-FU/LV gave hazard ratios of 0.88 (95% CI 0.77-1.01; p = 0.068) and 0.86 (95% CI 0.74-1.01; p = 0.060), respectively. The median follow-up at the time of analysis was 6.9 years. A predefined multivariate Cox analysis demonstrated superiority of capecitabineover bolus 5-FU/LV. The following factors were prespecified for inclusion in the statistical analysis plan:age, time from surgery to randomization, sex, baseline carcinoembryogenic antigen (CEA) levels, baseline lymph nodes, and country. For the entire randomized population, capecitabine was shown to be superior to 5FU/LV in terms of progression-free survival (hazard ratio 0.849; 95% CI: 0.739-0.976, p=0.0212) as well as in terms of overall survival (hazard ratio 0.828; 95% CI: 0.705-0.971, p=0.0203).

Adjuvant combination therapy in colon cancer

Data from a phase III, randomized, multicenter, controlled clinical trial (NO16968) in patients with stageIII colon cancer (Dukes Stage C) support the use of capecitabine in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer. In this trial, 944 patients were randomized to receive 3-week cycles for 24 weeks of capecitabine (1000 mg/m2 twice daily for 2 weeks followed by a 1-week rest period) in combination with oxaliplatin (130 mg/m2 intravenous infusion over 2 hours, administered on day 1, every 3 weeks); 942 patients were randomized to receivebolus 5-FU and leucovorin. In the primary analysis of DFS in the intention-to-treat population, XELOX
was shown to be significantly superior to 5-FU in the treatment of patients with stage III colon cancer (Dukes StageFU/LV (HR=0.80, 95% CI=[0.69; 0.93]; p=0.0045). The 3-year DFS value was 71% for XELOX versus
67% for 5-FU/LU. The analysis of the secondary objective of RFS supports these results with a HR of 0.78 (95% CI=[0.67; 0.92]; p=0.0024) for XELOX versus 5-FU/LV. XELOX showed a trend towards superior OS with a HR of 0.87 (95% CI=[0.72; 1.05]; p=0.1486), which translates to a 13% reduction inthe risk of death. The 5-year OS value was 78% for XELOX versus 74% for 5-FU/LV. Efficacy data arebased on a median observation time of 59 months for OS and

57 months for DFS. In the intention-to- treat population, the rate of discontinuations due to adverse events was higher in the XELOX combination treatment arm (21%) than in the 5FLU/LV monotherapy arm (9%).

Capecitabine monotherapy in metastatic colorectal cancer
Data from two identically designed controlled phase III clinical trials,
Multicenter, randomized trials (SO14695; SO14796) support the use of capecitabine for treatment in

first-line treatment for metastatic colorectal cancer. In these trials, 603 patients were randomized to capecitabine (1250 mg/m2 twice daily for 2 weeks followed by 1 week of rest, considered 3-week cycles).Another 604 patients were randomized to treatment with 5-
FU and leucovorin (Mayo regimen: 20 mg/m2 intravenous leucovorin followed by an intravenous bolus of 5-FU 425 mg/m2 on days 1 and 5, every 28 days). Objective overall response rates in the entire randomizedpopulation (investigator assessment) were 25.7% (capecitabine) versus 16.7% (Mayo regimen); p<0.0002.Median time to progression was 140 days (capecitabine) versus 144 days (Mayo regimen). Median survivalwas 392 days (capecitabine) versus 391 days (Mayo regimen).
Currently, there are no comparative data available on capecitabine monotherapy in colorectal cancer withfirst-line combination regimens.

Combination therapy in first-line treatment of metastatic colorectal cancer

Data from a multicenter, randomized, controlled phase III trial (NO16966) support the use of capecitabine incombination with oxaliplatin or in combination with oxaliplatin and bevacizumab for the first-line treatment ofmetastatic colorectal cancer. The trial had two stages: an initial stage with 2 arms where 634 patients wererandomized to two different treatment groups, including XELOX or FOLFOX-4, and a later stage with a 2x2factorial design in which 1401 patients were randomized to four different treatment groups that included XELOX + placebo, FOLFOX-4 + placebo, XELOX + bevacizumab, and FOLFOX-4 + bevacizumab. The different treatment regimens are included in Table 6.

Table 6 Treatment regimens in Trial NO16966 (mCRC)

	Treatment	**Initial Dose**	**Scheme**
FOLFOX-4 either	Oxaliplatin	85 mg/m2 intravenous for 2 h	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m2 intravenous for 2 h	Leucovorin on Day 1, every 2 weeks
	5-Fluorouracil	400 mg/m2 intravenous bolus, followed by 600 mg/m2 intravenous for 22 h	Days 1 and 2, every 2 weeks 5-fluorouracil intravenous bolus/ infusion, administered on Days 1and 2, every 2 weeks
FOLFOX-4 + Bevacizumab	Placebo or Bevacizumab	5 mg/kg intravenous over 30-90minutes	Day 1, prior to FOLFOX-

4, every 2 weeks			
XELOX	Oxaliplatin	130 mg/m2 intravenous for 2 h	Oxaliplatin on Day 1, every 3 weeks
either	Capecitabine	1000 mg/m2 orally twice daily day	Oral capecitabine twice daily for 2 weeks (followed by 1 week rest)
XELOX + Bevacizumab			
	Placebo or Bevacizumab	7.5 mg/kg intravenous over 30-90 minutes	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil:	intravenous bolus immediately after leucovorin		

In the overall comparison performed in the eligible patient population and in the intention-to-treat population,non-inferiority in terms of progression-free survival was demonstrated between the XELOX-containing arms and the FOLFOX-4-containing arms (see Table 7). The results indicate

that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see Table 7). A prespecified exploratory analysis was performed
comparing XELOX + bevacizumab versus FOLFOX-4 + bevacizumab. In this treatment subgroup comparison,XELOX + bevacizumab was similar to FOLFOX-4 + bevacizumab.

FOLFOX-4 + bevacizumab in terms of progression-free survival (hazard ratio 1.01; 97.5% CI 0.84, 1.22). Themedian follow-up at the time of the primary analyses in the intention-to-treat population was 1.5 years; data from the analysis after an additional year of follow-up are also included in Table 7. However, the on-treatmentprogression-free survival analysis did not confirm the results of the overall progression-free survival analysis and the overall survival analysis: the hazard ratio (HR) for XELOX versus FOLFOX-4 was 1.24 with a 97.5% confidence interval of 1.07-1.44. Although sensitivity analyses show that differences in regimen schedules and timing of tumour assessment influence the on-treatment progression-free survival analysis, a complete explanation for this result has not been found.

Table 7 Primary efficacy results from the non-inferiority analysis of Trial NO16966

	MAIN ANALYSIS		
	XELOX/XELOX+P/XELOX+BV (EPP*: N=967; ITT**: N=1017)	FOLFOX-4/FOLFOX-4+P/FOLFOX-4+BV (EPP*: N = 937; ITT**: N= 1017)	
Population	Median Time to Event (Days)		HR (97.5% CI)
Parameter: Progression-free survival			
PPE	ation	241	L ONE-YEAR FOLLOW-UP
PP		241	
E		244	Median Time to Event (Days)
ITT		244	
Parameter: Overall survival		581	
PPE 577			ADDITIONA
ITT			
Popul			

259			1.05 (0.94; 1.18)
259			1.04 (0.93; 1.16)
549			0.97 (0.84; 1.14)
553			0.96 (0.83; 1.12)
		HR (97.5% CI)	
Parameter: Progression-free survival			
P	24	25	1.02 (0.92; 1.14)
P	2	9	1.01 (0.91; 1.12)
E	24	25	
	4	9	1.00 (0.88; 1.13)
I			0.99 (0.88; 1.12)
T		59	
T	60	4	
	2	59	
Parameter: Overall survival		6	
EPP	600		
ITT			

*EPP=eligible patient population; **ITT=intention-to-treat population

Data from a randomized, controlled phase III trial (CAIRO) support the use of capecitabine at a starting dose of 1000 mg/m2 for 2 weeks in combination with irinotecan every 3 weeks for the first-line treatment of patientswith metastatic colorectal cancer. 820 patients were randomized to receive either sequential therapy (n=410) or combination therapy (n=410). Sequential therapy consisted of first-line treatment with capecitabine (1250mg/m2 twice daily for 14 days), second-line treatment with irinotecan (350 mg/m2 on day 1), and third-line combination therapy with capecitabine (1000 mg/m2 twice daily for 14 days) with oxaliplatin (130 mg/m2 on day 1). Combination treatment consisted of first-line treatment with capecitabine (1000 mg/m2 twice daily for 14 days) combined with irinotecan (250 mg/m2 on day 1)

(XELIRI) and in second line with capecitabine (1000 mg/m2 twice daily for 14 days) plus oxaliplatin (130 mg/m2 on day 1). All treatment cycles were administered at 3-week intervals. In the first-line treatment, the median progression-free survival in the intention-to-treat population was 5.8 months (95% CI 5.1 - 6.2 months)with capecitabine monotherapy and 7.8

months (95% CI 7.0 - 8.3 months; p=0.0002) with XELIRI.

However, this was associated with a higher incidence of gastrointestinal toxicity and neutropenia during first-line XELIRI treatment (26% and 11% for XELIRI and first-line capecitabine, respectively).

XELIRI has been compared to 5-FU + irinotecan (FOLFIRI) in three randomized studies in patients with metastatic colorectal cancer. XELIRI regimens include capecitabine 1000 mg/m2 twice daily for 14 days in a
3-week cycle in combination with irinotecan 250 mg/m2 on day 1. In the largest study (BICC-C study), patientswere randomized to receive open-label either FOLFIRI (n=144), bolus 5-FU (mIFL) (n=145), or XELIRI
(n=141) and were additionally randomized to receive either 5-FU + irinotecan (FOLFIRI) or 5-FU + irinotecan (FOLFIRI).

randomized to double-blind treatment with celecoxib or placebo. Median progression-free survival was 7.6 months in FOLFIRI, 5.9 months in mIFL (p=0.004 compared with FOLFIRI), and 5.8 months in XELIRI (p=0.015). Median overall survival was 23.1 months in FOLFIRI, 17.6 months in mIFL (p=0.09), and 18.9 months in XELIRI (p=0.27). Patients treated with XELIRI experienced excessive gastrointestinaltoxicity compared with FOLFIRI (diarrhea 48% and 14% in XELIRI and FOLFIRI, respectively).

In the EORTC study, patients were randomized to receive open-label FOLFIRI (n=41) or XELIRI (n=44) with an additional randomization to receive double-blind celecoxib or placebo. The median progression- free survival and overall survival were shorter for XELIRI than FOLFIRI (PFS 5.9 vs 9.6 months and OS 14.8 vs 19.9 months), and excess rates of diarrhea were reported in patients receiving the XELIRIregimen (41% XELIRI, 5.1% FOLFIRI).

In the study published by Skof et al., patients were randomized to receive either FOLFIRI or XELIRI treatment. The overall response rate was 49% in the XELIRI arm and 48% in the FOLFIRI arm (p = 0.76). At the end of treatment, 37% of patients in the XELIRI arm and 26% of patients in the FOLFIRI arm were disease-free (p = 0.56). Toxicity between treatments was similar except for neutropenia,which was reported more frequently in patients treated with FOLFIRI.

Monatgnani et al. used the results of the three previous studies to provide an overall analysis of randomized trials comparing FOLFIRI and XELIRI regimens in the treatment of metastatic colorectal cancer. It was associated with a significant reduction in therisk of progression with FOLFIRI (HR 0.76; 95% CI 0.62-0.95; p < 0.01), partly due to the poor tolerance of the XELIRI regimens used.

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Data from a randomized clinical trial (Souglakos et al, 2012) comparing treatment with FOLFIRI + bevacizumab versus XELIRI + bevacizumab treatment showed no differences significant differences in PFS or OS between both treatments. Patients were randomized to receive FOLFIRI plus bevacizumab (arm A, n=167) or XELIRI plus bevacizumab (arm B, n=166). In arm B, the XELIRI regimen used capecitabine 1000 mg/m2 twice daily for 14 days + irinotecan 250 mg/m2 on day 1. The median progression-free survival (PFS) was 10.0 and 8.9 months, p=0.64, overall survival 25.7 and 27.5 months, p=0.55, and response rate 45.5 and 39.8%, p=0.32 for FOLFIRI - Bev and XELIRI - Bev, respectively. Patients treated with XELIRI + bevacizumab had a significantly higher incidence ofdiarrhea, febrile neutropenia, and hand-foot syndrome than patients treated with FOLFIRI + bevacizumabwith a significant increase in treatment delays, dose reductions, and treatment interruptions.

Data from an interim analysis in a controlled phase II trial (AIO KRK 0604),
A multicenter, randomized trial supports the use of capecitabine at a starting dose of 800 mg/m2 for 2 weeks in combination with irinotecan and bevacizumab every 3 weeks in the first-line treatment of patients with metastatic colorectal cancer. 120 patients were randomized to receive the regimen Modified XELIRI with capecitabine 800 mg/m2 twice daily for two weeks followed by a 7-day rest period),irinotecan (200 mg/m2 infused over 30 minutes on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg infused over 30 to 90 minutes on day 1 every 3 weeks); 127 patients were randomized to treatment with capecitabine (1000 mg/m2 twice daily for two weeks followed by a 7-day rest period), oxaliplatin (130 mg/m2 infused over 2 hours on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg infused over 30 to 90 minutes on day 1 every 3 weeks). Due to the median duration of follow-up in the study population of 26.2months, responses to treatment were as follows:

Table 8 Key efficacy results from the AIO KRK study

	XELOX + bevacizumab (ITT: N=127)	Modified XELIRI + bevacizumab (ITT: N= 120)	Hazard ratio 95% IC P value
95% CI	69 - 84%	77 - 90%	
Progression-free survival at 6 months			
ITT 76%	84%		
Median progression-free survival			
ITT	10.4 months	12.1 months	0.93
95% CI	9.0 - 12.0	10.8 - 13.2	0.82 - 1.07
			P=0.30
The median overall survival			
ITT	24.4 months	25.5 months	0.90
95% CI	19.3 - 30.7	21.0 - 31.0	0.68 - 1.19
			P=0.45

Combination Therapy for the Second-Line Treatment of Metastatic Colorectal Cancer Data from a phase III, multicenter, randomized, controlled trial (NO16967) support the use of capecitabine in combination with oxaliplatin for the second-line treatment of metastatic colorectal cancer. In this trial,627 patients with metastatic colorectal carcinoma who had received prior treatment with irinotecan in combination with a fluoropyrimidine regimen as first-line therapy were randomized to receive either XELOX or FOLFOX-4. For the dosing schedule of XELOX and FOLFOX-4 (without the addition of placebo or bevacizumab), see Table 6. Non-inferiority of XELOX to FOLFOX-4 in terms of progression-free survival was demonstrated in both the per-protocol and intention-to-treat populations (see Table 9).

The results indicated that XELOX is equivalent to FOLFOX-4 in terms of overall survival (see Table 9).The median follow-up in the primary analyses in the intention-to-treat population was 2.1 years; data from analyses performed after an additional 6-month follow-up period are also included in Table 9.

Table 9 Primary efficacy results from the non-inferiority analysis of Trial NO16967

MAIN ANALYSIS			
	XELOX (PPP*: N=251; ITT**: N=313)	FOLFOX-4 (PPP*: N = 252; ITT**: N= 314)	
Population	Median Time to Event (Days)		HR (95% CI)
Parameter: Progression-free survival			
PPP	154	168	1.03 (0.87; 1.24)
ITT	144	146	0.97 (0.83; 1.14)
Parameter: Overall survival			
PPP 388		401	1.07 (0.88; 1.31)
ITT	363	382	1.03 (0.87; 1.23)
ADDITIONAL 6-MONTH FOLLOW-UP			
Population	Median Time to Event (Days)		HR (95% CI)
Parameter: Progression-free survival			
PPP	154	166	1.04 (0.87; 1.24)
ITT	143	146	0.97 (0.83; 1.14)
Parameter: Overall survival			
PPP	393	402	1.05 (0.88; 1.27)
ITT	363	382	1.02 (0.86; 1.21)

*PPP=per protocol population; **ITT=intention-to-treat population

Advanced gastric cancer:

Results from a multicenter, randomized, controlled phase III clinical trial in patients with advanced gastric cancer support the use of capecitabine for the first-line treatment of advanced gastric cancer (ML17032). In this trial, 160 patients were randomized to capecitabine (1000 mg/m2 twice daily for 2 weeks, followed by a 7-day rest period) and cisplatin (80 mg/m2 as a 2-hour infusion every 3 weeks). A total of 156 patients were randomized to 5-FU (800 mg/m2 per day, continuous infusion on days 1-5 every 3 weeks) and cisplatin (80 mg/m2 as a 2-hour infusion on day 1, every 3 weeks). Capecitabine in combination with cisplatin was non- inferior to 5-FU in combination with cisplatin in terms of progression-free survival in the per-protocol analysis(hazard ratio 0.81; 95% CI: 0.63–

1.04). The median progression-free survival was 5.6 months (capecitabine + cisplatin) versus 5.0 months (5-FU + cisplatin). The hazard ratio for survival duration (overall survival) was similar to the hazard ratio for progression-free survival (hazard ratio 0.85; 95% CI: 0.64–1.13). The median survival duration was 10.5 months (capecitabine + cisplatin) versus 9.3 months (5-FU + cisplatin).

The results of a multicenter, randomized phase III trial comparing capecitabine with 5-FU and oxaliplatin withcisplatin in patients with advanced gastric cancer support the use of Capecitabine for the first-line treatment of advanced gastric cancer (REAL-2). In this trial, using a factorialdesign, 1002 patients were randomized 2x2 to each of the following 4 arms:

- ECF: epirubicin (50 mg/ m2 as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m2 as a two-hourinfusion on day 1 every 3 weeks), and 5-FU (200 mg/m2 administered daily by continuous infusion through a central line).
- ECX: epirubicin (50 mg/m2 as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m2 as a 2-hour infusion on day 1 every 3 weeks), and capecitabine (625 mg/m2 twice daily

continuously).

- EOF: epirubicin (50 mg/m2 as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m2 administered as a 2-hour infusion on day 1 every three weeks), and 5-FU (200 mg/m2 administereddaily by continuous infusion through a central line).
- EOX: epirubicin (50 mg/m2 as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m2 administered as a 2-hour infusion on day 1 every three weeks), and capecitabine(625 mg/m2 twice daily continuously).

The primary efficacy analyses in the per-protocol population demonstrated non-inferiority of capecitabine versus 5-FU-based regimens (hazard ratio 0.86; 95% CI: 0.8–0.99) and oxaliplatin versus cisplatin-based regimens (hazard ratio 0.92; 95% CI: 0.80–1.1). The median overall survival was 10.9 monthsin capecitabine-based regimens and 9.6 months in 5-FU-based regimens. The median overall survival was 10.0 months in cisplatin-based regimens and 10.4 months in oxaliplatin-based regimens.

Capecitabine has also been used in combination with oxaliplatin for the treatment of cancer. advanced gastric cancer. Trials with capecitabine monotherapy indicate that capecitabine has activity inadvanced gastric cancer.

Advanced colon, colorectal and gastric cancer: a meta-analysis
A meta-analysis of six clinical trials (trials SO14695, SO14796, M66001, NO16966, NO16967, M17032) supports the use of capecitabine as a replacement for 5-FU as monotherapy and in combination therapy in gastrointestinal cancer. The pooled analysis includes 3097 patients treated with capecitabine- containing regimens and 3074 patients treated with 5-FU-containing regimens. The median overall survival time was 703 days (95% CI: 671, 745) in patients treated with capecitabine-containing regimens and 683 days(95% CI: 646, 715) in patients treated with 5-FU-containing regimens. The hazard ratio for overall survival was 0.94 (95% CI: 0.89, 1.00; p=0.0489) indicating that capecitabine-containing regimens are noninferior to 5-FU-containing regimens.

Breast cancer:

Combination therapy with capecitabine and docetaxel in locally advanced breast cancer ormetastatic

Data from a multicenter, randomized, controlled phase III clinical trial support the use of capecitabine incombination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancerafter failure of cytotoxic therapy including an anthracycline.

In that trial, 255 patients were randomized to capecitabine (1250 mg/m2 twice daily for 2 weeks followed by 1week rest and docetaxel 75 mg/m2 intravenously infused over 1 hour every 3 weeks). An additional 256 patients were randomized to docetaxel alone (100 mg/m2 intravenously infused over 1 hour every 3 weeks). Survival was longer in the combination capecitabine + docetaxel arm (p=0.0126). Median survival was 442 days (capecitabine + docetaxel) versus 352 days (docetaxel alone). Overall objective response rates in the entire randomized population (investigator assessment) were 41.6% (capecitabine + docetaxel) versus 29.7% (docetaxel alone); p=0.0058. The time to disease progression was longer in the arm treated with the capecitabine + docetaxel combination (p<0.0001). The median time to progression was 186 days (capecitabine + docetaxel) versus 128 days (docetaxel alone).

Capecitabine monotherapy after failure of taxanes, anthracycline-containing chemotherapy or forthose patients in whom anthracycline therapy is not

indicated
Data from 2 multicenter phase II clinical trials support the use of capecitabine monotherapy for the treatmentof patients who have not responded to taxanes or an anthracycline-based chemotherapy regimen or who cannot be subsequently treated with anthracyclines. In these trials,
trials, a total of 236 patients were treated with capecitabine (1250 mg/m2 twice daily for 2 weeks followed bya 1-week rest period). The overall objective response rates (investigator assessment) were 20% (first trial)and 25% (second trial). The median time to progression was 93 and 98 days. The median survival was 384 and 373 days.

All indications:

In a meta-analysis of 14 clinical trials with data from more than 4,700 patients treated with Capecitabine monotherapy or capecitabine in combination with different chemotherapy regimens in

multiple indications (colon, colorectal, gastric and breast cancer) it was shown that patients treated with capecitabine who developed hand-foot syndrome had a longer overall survival compared to patients who did not develop hand-foot syndrome: median overall survival of 1100 days (95% CI: 1007 - 1200) versus 691 days (95% CI: 638 - 754) with a hazard ratio of 0.61
(95% CI: 0.56 - 0.66).

Pediatric population

The European Medicines Agency has waived the obligation to conduct studies with Xeloda in all subsets of the paediatric population in adenocarcinoma of the colon and rectum,
gastric adenocarcinoma and breast carcinoma (see section 4.2 for information on use in the paediatric population).

5.2. Pharmacokinetic properties

The pharmacokinetics of capecitabine have been evaluated over the dose range of 502-3,514 mg/m2 /day. The parameters of capecitabine, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5'-DFUR) measured on days 1 and 14 were similar. The AUC of 5-FU increased by 30-35% on day 14. Dose reduction of capecitabine decreases systemic exposure to 5-FU by a greater than dose proportion ratio due to non-linear pharmacokinetics of the active metabolite.

Absorption

Following oral administration, capecitabine crosses the intestinal mucosa as an intact molecule and is rapidly and extensively absorbed, subsequently being extensively transformed into the 5'-metabolites
DFCR and 5'-DFUR. Administration with food reduces the rate of absorption of capecitabine but only minimally modifies the AUC of 5'-DFUR and the AUC of the subsequent metabolite, 5-
FU. At the dose of 1250 mg/m2 on day 14 administered after food, the maximum plasma concentrations (Cmax in ÿg/ml) for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 4.67, 3.05, 12.1, 0.95 and 5.46 respectively. The times to maximum plasma concentrations (Tmax in hours) were 1.50, 2.00, 2.00, 2.00 and 3.34. The AUC0ÿÿ values in ÿgh/ml were 7.75, 7.24,
24.6, 2.03 and

36.3.

Distribution

In vitro studies with human plasma have revealed that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU binds to proteins, mainly albumin, at 54%, 10%, 62% and 10%, respectively.

Metabolism or Biotransformation

First, capecitabine is metabolized by hepatic carboxyesterase into 5'-DFCR, which is Capecitabine is then transformed into 5'-DFUR by cytidine deaminase, which is primarily located in the liver and tumor tissues.Catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are localized in tumor tissues but are also present in healthy tissues, but usually at lower levels. The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations within tumor tissues. In colorectal tumors,5-FU generation is mostly localized in tumor stromal cells. After oral administration of capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumor to plasma was 21.4 (ranged from 3.9 to 59.9, n=8), while the ratio between healthy tissues and plasma was 8.9 (ranged from 3.0 to 25.8, n=8). Thymidine phosphorylase activity was measured and found to be 4-fold higher in primary colorectal tumor than in adjacent normal tissue. According to the studies

Immunohistochemically, thymidine phosphorylase is localized to a greater extent in tumor stromal cells.

5-FU is subsequently catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD) to dihydro-5-fluorouracil (FUH2) which is much less toxic. Dihydropyrimidinase cleaves the pyrimidine ring and produces 5-fluoro-ureidopropionic acid (FUPA). Finally, ÿ-ureidopropionase transforms FUPA to ÿ-fluoro-ÿ-alanine (FBAL) which is eliminated in urine.
Dihydropyrimidine dehydrogenase (DPD) activity is the rate-limiting step. Deficiency in DPD may lead to increased toxicity of capecitabine (see sections 4.3 and 4.4).

Elimination

The elimination half-life (t1/2 in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL was 0.85,1.11, 0.66, 0.76 and 3.23 respectively.
Capecitabine metabolites are primarily eliminated by urinary excretion. 95.5% of the administered dose of capecitabine is recovered in urine. Excretion Fecal excretion is minimal (2.6%). The main metabolite excreted in urine is FBAL, representing 57% of theadministered dose.
Approximately 3% of the administered dose is excreted unchanged in urine.

Combination therapy
Phase I trials to evaluate the effect of capecitabine on the pharmacokinetics of docetaxel or paclitaxel and vice versa showed that there is no effect of capecitabine on the pharmacokinetics of docetaxel or paclitaxel(Cmax and AUC) of either docetaxel or paclitaxel on the pharmacokinetics of 5'-DFUR.

Pharmacokinetic/pharmacodynamic data(s)

A population pharmacokinetic analysis was performed following treatment with capecitabine in 505 patients withcolorectal cancer at a dose of 1250 mg/m2 twice daily. Sex, presence or absence of baseline liver metastases, Karnofsky score, total bilirubin, serum albumin, AST and ALT had no statistically significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

Patients with hepatic insufficiency due to liver metastases. Based on a pharmacokinetic studyperformed in cancer patients with mild to moderate liver failure caused by metastasis
In patients with hepatic impairment, the bioavailability of capecitabine and exposure to 5-FU may be increased
compared to patients without hepatic impairment. Pharmacokinetic data are not available in patients with hepatic impairment.severe liver failure.

Patients with renal impairment. Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment, there is no evidence of an effect of creatinine clearance on

the pharmacokinetics of the intact drug and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5'-DFUR (35% increase in AUC when creatinine clearance decreased by 50%) and FBAL (114% increase in AUC when creatinine clearance decreased by 50%). FBAL is a metabolite without antiproliferative activity.

Elderly patients. Based on population pharmacokinetic analyses, which included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients aged In patients aged 65 years or older, age did not influence the pharmacokinetics of 5'-DFUR or 5-FU. The AUC of FBAL increased with age (20% increase in age results in a 15% increase in FBAL AUC). This increase is probably due to a change in renal function.

Ethnic factors. Following oral administration of 825 mg/m2 capecitabine twice daily for 14 days, Japanese patients (n=18) had approximately 36% lower Cmax and 24% lower AUC of capecitabine than Caucasian patients (n=22). Japanese patients also had 25% lower Cmax and 34% lower AUC of FBAL than Caucasian patients. The clinical relevance of these differences is unknown. No significant differences in exposure to other metabolites (5'-DFCR, 5'-DFUR and 5-FU) were observed.

5.3. Preclinical safety data

In multiple-dose toxicity studies, daily oral administration of capecitabine to cynomolgus monkeys and mice was associated with toxic effects on the gastrointestinal, lymphoid and hematopoietic systems, typical of fluoropyrimidines. These toxic effects were reversible. Cutaneous toxicity, characterized by degenerative/ regressive changes, has been observed with capecitabine. Capecitabine did not cause hepatic or CNS toxicity.Cardiovascular toxicity (e.g., prolongation of PR and QT intervals) was detected in cynomolgus monkeys following intravenous administration (100 mg/kg) but not following repeated oral administration (1379 mg/m2 / day).

A two-year carcinogenicity study in mice found no evidence of carcinogenicity with capecitabine.

During standard fertility studies, impaired fertility was observed in female mice treated with capecitabine; however, this effect was reversible after a therapeutic break. In addition, during a 13-week study, degenerative and atrophic changes occurred in the reproductive organs of male mice; however, these effects were reversibleafter a therapeutic break (see section 4.6).

In embryotoxicity and teratogenicity studies in mice, a dose-related increase in fetal resorptions and teratogenicity was observed. At high doses, abortions and embryonic deaths were observed in monkeys, butno signs of teratogenicity.

Capecitabine was not mutagenic *in vitro* for bacteria (Ames test) or mammalian cells (Chinese hamster V79/ HPRT gene mutation assay). However, as with other nucleoside analogues (e.g. 5-FU), capecitabine showed a clastogenic effect on human lymphocytes *(in vitro)* and a positive trend in murine bone marrow micronucleustests (in vivo).

6. PHARMACEUTICAL DATA

6.1. List of excipients

Tablet core:
anhydrous
lactose,
croscarmellose
sodium
(E468),
hypromellose
(E464),
microcrystalline cellulose (E460),
magnesium stearate.

Tablet coating:
Polyvinyl
alcohol
(E1203),

titanium
dioxide
(E171),
Polyethyle
ne
glycol/mac
rogol
yellow
iron oxide
(E172) red
iron oxide
(E172),
black iron
oxide
(E172)talc

6.2. Incompatibilities

Not applicable

6.3.Shelf Life

Two Years

6.4. Special precautions for storage

Do not store at a temperature above 30ºC

6.5. Nature and contents of the container

Each pack contains 120 film-coated tablets.

6.6. Special precautions for disposal and other handling

Any unused medicinal product and any materials that have been in contact with it should be disposed ofin accordance with local regulations for cytostatics.

7. MARKETING AUTHORIZATION HOLDER

Merixil Pharma
Office No 28, 2nd
Floor, Rose PlazaI-8
Markaz, Islamabad.

MANUFACTURED BY

NORMON LABORATORIES, S.A.
C/ Ronda de
Valdecarrizo,
628760 Tres
Cantos,
Madrid Spain

8.REGISTRATION NUMBER / MARKETING AUTHORISATION NUMBER

081801

9. DATE OF FIRST MARKET AUTHORIZATION / RENEWAL OF REGISTRATION

Date of first Registration / Market
Authorization:15th Sep 2016Date of
latest renewal: 14th Sep 2026

10. DATE OF TEXT REVISION