Package Insert

INTACAPE 150 (Capecitabine Tablets USP 150 mg)

a) Name and Strength of Active Substance

Each film coated tablet contains:
Capecitabine USP 150 mg

b) Product Description

Light peach coloured, oblong shaped, biconvex, film coated tablets, debossed with '150' on one side and plain on other side.

c) Pharmacodynamics/ Pharmacokinetics

Pharmacodynamic properties

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel.

There is evidence that the metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby interfering with the synthesis of deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU may be to create a thymidine deficiency that provokes unbalanced growth and death of a cell. The effects of DNA and RNA deprivation are most marked on those cells which proliferate more rapidly and which metabolise 5-FU at a more rapid rate.

Pharmacokinetic properties

Absorption: After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites, 5'-DFCR and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption,

Metabolism: Capecitabine is first metabolized by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are found in tumour tissues but also in normal tissues, albeit usually at lower levels. The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations within tumour tissues. In the case of colorectal tumours, 5-FU generation appears to be in large part localised in tumour stromal cells.

5-FU is further catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β-ureido-

propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate limiting step. Deficiency of DPD may lead to increased toxicity of capecitabine.

Elimination: Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Faecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL, which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

Pharmacokinetics in special populations: Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT do not have significant effect on the pharmacokinetics of 5' – DFUR, 5-FU and FBAL.

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

Patients with renal impairment: In cancer patients with mild to severe renal impairment, there is no evidence for an effect of creatinine clearance on the pharmacokinetics of intact drug and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5'-DFUR and to FBAL is a metabolite without antiproliferative activity.

Elderly: Patients greater or equal to 65, age has no influence on the pharmacokinetics of 5'-DFUR and 5-FU. The AUC of FBAL increased with age. This increase is likely due to a change in renal function.

d) Indication

Breast Cancer:
Intacape in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Intacape is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of a taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Intacape is indicated in combination with lapatinib ditosylate for the treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2 and who have received prior therapy including an anthracycline, a taxane and trastuzumab.

Colon, Colorectal cancer:
Intacape is indicated for the treatment of patients with metastatic colorectal carcinoma.
Intacape is indicated as adjuvant treatment of patients following surgery of Stage III (Duke's Stage C) colon cancer.

Oesophagogastric Cancer:
Intacape is indicated as first-line treatment of patients with advanced oesophagogastric cancer in combination with a platinum-based regimen.

e) Recommended Dosage

Standard dosage
Intacape tablets should be swallowed with water within 30 minutes after a meal.

Monotherapy:
Colon, Colorectal and breast cancer
The recommended monotherapy starting dose of Intacape is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 7-day rest period.

Combination therapy
Breast Cancer
In combination with docetaxel
In combination with docetaxel, the recommended dose of Intacape is 1250 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks.
Pre-medication according to the docetaxel labelling, should be started prior to docetaxel administration for patients receiving the Intacape plus docetaxel combination.

In combination with lapatinib ditosylate
In combination with lapatinib ditosylate, the recommended dose of Intacape is 2000 mg/m^2/day administered orally in 2 doses 12 hours apart for 14 days (Day 1-14) in a repeating 21 day cycle combined with lapatinib ditosylate 1250 mg (5 tablets) given orally once daily from Day 1-21. (See manufacturer's prescribing information for lapatinib ditosylate for further information).

Colon, colorectal cancer
In combination with oxaliplatin and/or bevacizumab
In combination with oxaliplatin and/or bevacizumab the recommended dose of Intacape is 1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period. The first dose of Intacape is given on the evening of day 1 and the last dose is given on the morning of day 15. Given as a 3-weekly schedule, on day 1 every 3 weeks bevacizumab is administered as a 7.5mg/kg intravenous infusion over 30-90 minutes followed by oxaliplatin administered as a 130 mg/m^2 intravenous infusion over 2 hours.
Premedication to maintain adequate hydration and anti-emesis according to the oxaliplatin product information should be started prior to oxaliplatin administration for patients receiving the Intacape plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Oesophagogastric Cancer
In combination with platinum-based regimen:
In combination with a platinum-based compound the recommended dose of Intacape for the treatment of advanced Oesophagogastric cancer is 1000 mg/m^2 administered twice daily for 14 days followed by a 7 day rest period. The first dose of Intacape should be given on the evening of day 1 and the last dose should be given on the morning of day 15. If epirubicin is added to this regimen the recommended dose of Intacape is 625 mg/m^2 twice daily continuously. Epirubicin at a dose of 50 mg/m^2 should be given as a bolus on day 1 every 3 weeks. The platinum based compound (cisplatin at a dose of 60 mg/m^2 (triple regimen) - 80 mg/m^2 (double regimen) or oxaliplatin at a dose of 130 mg/m^2) should be given on day 1 as a 2 hour intravenous infusion every 3 weeks.

Premedication to maintain adequate hydration and anti-emesis according to the cisplatin/oxaliplatin summary of product characteristics should be started prior to cisplatin/oxaliplatin administration for patients receiving the Intacape plus cisplatin/oxaliplatin combination

Intacape dose is calculated according to body surface area.The following tables show the standard and reduced dose calculations (see section "*Dosage adjustments during treatment*") for a starting dose of Intacape of either 1250mg/m^2 or 1000mg/m^2.

Table 1 Standard and reduced dose calculations according to body surface area for a starting dose of Capecitabine Tablets of 1250 mg/m^2

	Dose level 1250 mg/m^2 (twice daily)				
	Full dose 1250 mg/m^2	Number of tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 950 mg/m^2	Reduced dose (50%) 625 mg/m^2
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	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
≥2.19	2800	2	5	2150	1450

Table 2 Standard and reduced dose calculations according to body surface area for a starting dose of Capecitabine Tablets of 1000 mg/m^2

	Dose level 1000 mg/m^2 (twice daily)				
	Full dose 1000 mg/m^2	Number of tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 750 mg/m^2	Reduced dose (50%) 500 mg/m^2
Body	Dose per	150 mg	500 mg	Dose per	Dose per

Surface Area (m^2)	administration (mg)			administration (mg)	administration (mg)
≤ 1.26	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
≥ 2.19	2300	2	4	1750	1100

Dosage adjustments during treatment
General:
Toxicity due to Intacape administration may be managed by symptomatic treatment and/or modification of the Intacape dose (treatment interruption or dose reduction). Once the dose has been reduced it should not be increased at a later time.
For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening treatment can be continued at the same dose without reduction or interruption.

Dosage modifications are not recommended for Grade 1 events. Therapy with Intacape should be interrupted if a Grade 2 or 3 adverse experience occurs. Once the adverse event has resolved or decreased in intensity to Grade 1, Intacape therapy may be restarted at full dose or as adjusted according to Table 3. If a Grade 4 experience occurs, therapy should be discontinued or interrupted until the experience has resolved or decreased to Grade 1, and therapy should be restarted at 50% of the original dose. Patients taking Intacape should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of Intacape omitted for toxicity are not replaced

Haematology:
Patients with baseline neutrophil counts of <1.5 X 10^9/L and/or thrombocyte counts of <100 X 10^9/L should not be treated with Intacape. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 haematologic toxicity, treatment with Intacape should be interrupted.
The following table shows the recommended dose modifications following toxicity related to with Intacape:

Table 3 Capecitabine Tablets Dose Reduction Schedule

Toxicity NCIC grades*	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose (% of starting dose)**
• Grade 1	Maintain dose level	Maintain dose level
• Grade 2		
-1st appearance	Interrupt until resolved to grade	100%

-2nd appearance	0-1	75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• Grade 3		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• Grade 4		
-1st appearance	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd appearance	Discontinue permanently	Not applicable

*According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. For hand-foot syndrome and hyperbilirubinemia. *(see section Warnings and Precautions).*

The following are the recommended dose modifications for toxicity when Capecitabine and docetaxel are used in combination:

Table 4: Intacape (X) in combination with docetaxel (T) dose reduction schedule

	Recommended Dose Modifications	
	Capecitabine dose changes within a treatment cycle	
Toxicity grade[1]	**Grade 1**	
	100% of starting dose (no interruption)	X: 100% of starting dose T: 100% (75 mg/m^2)
Toxicity grade[1]	**Grade 2**	
1st appearance	Interrupt until resolved (grade 0 – 1)	X: 100% of starting dose T: 100% (75mg/m^2)
2nd appearance of same toxicity	Interrupt until resolved (grade 0 – 1)	X: 75% of starting dose T: Reduce to 55mg/m^2
3rd appearance of same toxicity	Interrupt until resolved (grade 0 – 1)	X: 50% of starting dose **T: Discontinue permanently**
4th appearance of same toxicity	**Discontinue permanently**	
Toxicity grade	**Grade 3**	

	If grade 3 haematological see section on haematological toxicity, otherwise:	
1st appearance	Interrupt until resolved (grade 0 – 1)	X: 75% of starting dose T: Reduce to 55 mg/m^2
2nd appearance	Interrupt until resolved (grade 0 – 1)	X: 50% of starting dose **T: Discontinue permanently**
3rd appearance	**Discontinue permanently**	
Toxicity grade[1]	**Grade 4**	
	If G4 haematological see section on haematological toxicity, otherwise:	
1st appearance	Discontinue permanently *or* (if physician deems it to be in the best of interest of the patient) interrupt until resolved (grade 0-1)	X: Reduce to 50% **T: Discontinue permanently**
2nd appearance	**Discontinue permanently**	

*National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-foot syndrome *(see section Warnings and Precautions).*

Specific dose adjustment in combination with docetaxel
Intacape and/or docetaxel dose modifications should be made according to the general dose modification scheme above, if nothing else is stated regarding specific dose adjustments. For those toxicities considered unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption. At the beginning of a treatment cycle, if either a docetaxel or a Intacape treatment delay is indicated, both docetaxel and Intacape administration should be delayed until the requirements for restarting both drugs are met. If docetaxel has to be discontinued, Intacape treatment can be resumed when the requirements for restarting Intacape are met.

Hematology: Treatment should only be re-administered when the neutrophil count is ≥1.5 x 10^9/l (Grade 0 - 1). Patients with neutropenia <0.5 x 10^9/l (Grade 4) for more than 1 week, or febrile (>38°C) neutropenia, should have the docetaxel dosage reduced from 75 mg/m^2 to 55 mg/m^2. If Grade 4 neutropenia or febrile neutropenia occurs at 55 mg/m^2 docetaxel, docetaxel should be discontinued. Patients with baseline neutrophil counts of <1.5 x 10^9/l and/or thrombocyte counts of <1.0 x 10^9/l should not be treated with the Intacape/docetaxel combination.

Hypersensitivity: Patients who develop severe hypersensitivity reactions (hypotension with a decrease of ≥20 mm Hg, or bronchospasm, or generalised rash/erythema) should stop treatment immediately and be given appropriate therapy. These patients should not be re challenged with the drug suspected to have caused hypersensitivity.

Peripheral neuropathy: For 1st appearance of Grade 2 toxicity, reduce the docetaxel dose to 55 mg/m^2. If Grade 3 toxicity appears, discontinue docetaxel treatment. In both instances follow the above dose modification scheme for Intacape.

Fluid retention: Severe (Grade 3 or 4) toxicity such as pleural effusion, pericardial effusion or ascites which is possibly related to docetaxel should be closely monitored. In case of

appearance of such toxicity docetaxel treatment should be discontinued, Intacape treatment may be continued without dose modification.

Hepatic impairment: Docetaxel should generally not be given to patients with serum bilirubin above the upper limit of normal. The following modifications should be applied to the docetaxel dose in the event of abnormal values for ASAT, ALAT, and/or alkaline phosphatase levels:

Table 5: Modifications to the docetaxel dose

ASAT and/or ALAT values		**Alkaline phosphatase values**	**Docetaxel dose modification**
≤1.5 x UNL	and	≤5 x UNL	no dose modification
>1.5 x UNL — ≤2.5 x UNL	and	≤2.5 x UNL	no dose modification
>2.5 x UNL — ≤5 x UNL	and	≤2.5 x UNL	reduce by 25% (not below 55 mg/m^2)
>1.5 x UNL — ≤5 x UNL	and	>2.5 x UNL — ≤5 x UNL	reduce by 25% (not below 55 mg/m^2)
>5 x UNL	or	>5 x UNL (unless bone metastases are present in the absence of any liver disorder)	delay dose by a maximum of 2 weeks. If no recovery, discontinue docetaxel.

Once the docetaxel dose is reduced for a given cycle, no further dose reduction is recommended for subsequent cycles unless worsening of the parameters is observed. In case of recovery of liver function tests after previous reduction of the docetaxel dose, the docetaxel dose can be re-escalated to the previous dose level.

Dehydration: Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. If Grade 2 (or higher) dehydration occur, Intacape treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be those for the precipitating adverse event in accordance with the above guidelines.

Reductions to 75% and 50% of Intacape *dose*

For patients receiving Intacape monotherapy or Intacape in combination with docetaxel, the following tables show the dosage at 75% and 50%, calculated according to the body surface area:

Table 6: Calculated Intacape dose, reduced to 75% of the standard starting dose

Dose level 950 mg/m^2 twice daily		**Number of tablets administered in the morning**		**Number of tablets administered in the evening**	
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.26	1150	1	2	1	2
1.27 – 1.38	1300	2	2	2	2
1.39 – 1.52	1450	3	2	3	2
1.53 – 1.66	1500	–	3	–	3

Dose level 950 mg/m² twice daily		**Number of tablets administered in the morning**		**Number of tablets administered in the evening**	
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
1.67 – 1.78	1650	1	3	1	3
1.79 – 1.92	1800	2	3	2	3
1.93 – 2.06	1950	3	3	3	3
2.07 – 2.18	2000	–	4	–	4
≥2.19	2150	1	4	1	4

Calculated Intacape dose, reduced to 50% of the standard starting dose

Dose level 625 mg/m² twice daily		**Number of tablets administered in the morning**		**Number of tablets administered in the evening**	
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.38	800	2	1	2	1
1.39 – 1.52	950	3	1	3	1
1.53 – 1.66	1000	–	2	–	2
1.67 – 1.78	1000	–	2	–	2
1.79 – 1.92	1150	1	2	1	2
1.93 – 2.06	1300	2	2	2	2
2.07 – 2.18	1300	2	2	2	2
≥2.19	1450	3	2	3	2

Special dosage instructions

Patients with hepatic impairment due to liver metastases

In patients with mild to moderate hepatic impairment due to liver metastases, no starting dose adjustment is necessary. However, such patients should be carefully monitored *(see section Pharmacokinetics in Special Populations and section Warnings and Precautions)*.Patients with severe hepatic impairment have not been studied.

Patients with renal impairment

In patients with moderate renal impairment (creatinine clearance 30 -50 ml/min [Cockroft and Gault]) at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m^2 is recommended. In patients with mild renal impairment (creatinine clearance 51-80 ml/min), no adjustment in starting dose is recommended.

Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3, or 4 adverse event with subsequent dose adjustment as outlined in Table 3 above *(see also section Pharmacokinetics in Special Populations)*. If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, Intacape should be discontinued. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use. For dosage calculations, see Table 1 and Table 2.

Children

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

Elderly

- For Intacape monotherapy, no adjustment of the starting dose is needed. However severe Grade 3 or 4 treatment-related adverse events were more frequent in patients over 80 years of age compared to younger patients.

When Intacape was used in combination with other agents, elderly patients (≥65 years) experience more Grade 3 and Grade 4 adverse drug reactions (ADRs) and ADRs that led to discontinuation, than younger patients. Careful monitoring of elderly patients is advisable.

- In combination with docetaxel, an increased incidence of Grade 3 or 4 treatment-related adverse events and treatment-related serious adverse events was observed in patients 60 years of age or more. For patients 60 years of age or more treated with the combination of Intacape plus docetaxel, a starting dose reduction of Intacape to 75% (950 mg/m^2 twice daily) is recommended. For dosage calculations, see Table 2.

In combination with irinocetan: for patients 65 years of age or more, a starting dose reduction of Intacape to 800 mg/m^2 twice daily is recommended.

f) Route of Administration : Oral

g) Contraindications

Intacape is contraindicated in patients with known hypersensitivity to capecitabine or to any of its components.

Intacape is contraindicated in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil.

As with other fluoropyrimidines, Intacape is contraindicated in patients with known DPD (dihydropyrimidine dehydrogenase) deficiency.

Intacape should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine.

Intacape is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min).

If contraindications exist to any of the agents in a combination regimen, that agent should not be used.

h) Warnings and Precautions

Dose limiting toxicities

Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia). Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.

Diarrhoea

Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrhoeal treatments (e.g. loperamide) may be used. NCIC CTC grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and

malabsorption. Grade 4 diarrhoea is an increase of ≥10 stools/day or grossly bloody diarrhoea or the need for parenteral support. Dose reduction should be applied as necessary.

Dehydration

Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic drugs. Acute renal failure secondary to dehydration might be potentially fatal. If grade 2 (or higher) dehydration occurs, capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications should be applied for the precipitating adverse event as necessary.

Hand-foot syndrome

Hand and foot syndrome also known as hand-foot skin reaction or 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/or feet and/or discomfort which does not disrupt the patient's normal activities.

Grade 2 hand-foot syndrome is painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.

Grade 3 hand-foot syndrome is moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. Persistent or severe hand-foot syndrome (Grade 2 and above) can eventually lead to loss of fingerprints which could impact patient identification. If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased. When capecitabine and cisplatin are used in combination, the use of vitamin B6 (pyridoxine) is not advised for symptomatic or secondary prophylactic treatment of hand-foot syndrome, because of published reports that it may decrease the efficacy of cisplatin. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with Capecitabine.

Cardiotoxicity

Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation). These adverse reactions may be 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 receiving capecitabine.

Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris.

Hypo- or hypercalcaemia

Hypo- or hypercalcaemia has been reported during capecitabine treatment. Caution must be exercised in patients with pre-existing hypo- or hypercalcaemia.

Central or peripheral nervous system disease

Caution must be exercised in patients with central or peripheral nervous system disease, e.g. brain metastasis or neuropathy.

Diabetes mellitus or electrolyte disturbances

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

Coumarin-derivative anticoagulation

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

Brivudine. Brivudine must not be administered concomitantly with capecitabine. Fatal cases have been reported following this drug interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of capecitabine therapy. Treatment with brivudine can be started 24 hours after the last dose of capecitabine. 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. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

Hepatic impairment

In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of >3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of >2.5 x ULN occur. Treatment with capecitabine monotherapy may be resumed when bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

Renal impairment

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

Dihydropyrimidine dehydrogenase (DPD) deficiency

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity.

Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Although DPD deficiency cannot be precisely defined, it is known that patients with certain homozygous or certain compound heterozygous mutations in the *DPYD (Dihydropyrimidine dehydrogenase)* gene locus (e.g. DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants), which can cause complete or near complete absence of DPD enzymatic activity (as determined from laboratory assays), have the highest risk of life-threatening or fatal toxicity and should not be treated with Capecitabine. No dose has been proven safe for patients with complete absence of DPD activity.

Patients with certain heterozygous DPYD variants (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have increased risk of severe toxicity when treated with capecitabine.

The frequency of the heterozygous DPYD*2A genotype in the DPYD gene in Caucasian patients is around 1%, 1.1% for c.2846A>T, 2.6-6.3% for c.1236G>A/HapB3 variants and 0.07 to 0.1% for c.1679T>G. Genotyping for these alleles is recommended to identify patients at increased risk for severe toxicity. Data on the frequency of these DPYD variants in other populations than Caucasian is limited. It cannot be excluded that other rare variants may also be associated with an increased risk of severe toxicity.

For patients with partial DPD deficiency (such as those with heterozygous mutations in the *DPYD* gene) and where the benefits of Capecitabine are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution and frequent monitoring with dose adjusment according to toxicity. A reduction of the starting dose in these patients may be considered to avoid serious toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by specific test. It has been reported that the DPYD*2A, c.1679T>G variants lead to a greater reduction in enzymatic activity than the other variants with a higher risk of side effects. The consequences of a reduced dose for efficacy are currently uncertain. Therefore, in the absence of serious toxicity the dose could be increased while carefully monitoring the patient.

The patients who are tested negative for the above-mentioned alleles may still have a risk of severe adverse events.

In patients with unrecognised DPD deficiency treated with capecitabine, as well as in those patients who test negative for specific *DPYD* variations, life-threatening toxicities manifesting as acute overdose may occur. In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities.

Ophthalmologic complications

Patients should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated as clinically appropriate.

Severe skin reactions

Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. Capecitabine should be permanently discontinued in patients who experience a severe skin reaction during treatment.

Excipients

As this medicinal product contains anhydrous lactose as an excipient, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ability to Drive or Operate Machines

Driving and using machines INTACAPE may make you feel dizzy, nauseous or tired. It is therefore possible that INTACAPE could affect your ability to drive a car or operate machines.

i) Interactions with Other Medicaments

Coumarin anticoagulants

Altered coagulation parameters and/or bleeding have been reported in patients taking Intacape concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating Intacape therapy and, in a few cases, within one month after stopping Intacape.

Patients taking coumarin-derivative anticoagulants concomitantly with Intacape should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anti-coagulant dose adjusted accordingly.

Cytochrome P450 2C9 substrates

No formal drug-drug interaction studies with capecitabine and other drugs known to be metabolized by the cytochrome and other drugs known to be metabolized by the cytochrome P450 2C9 isoenzyme have been conducted. Care should be exercised when Intacape is co-administered with these drugs.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of Intacape with phenytoin.

Patients taking phenytoin concomitantly with Intacape should be regularly monitored for increased phenytoin plasma concentrations.

Drug-food interaction

Since current safety and efficacy data are based upon administration with food, it is recommended that Intacape be administered with food.

Antacid

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

Leuconvorin folinic acid

The effect of leucovorin on the pharmacokinetics of Intacape was investigated in cancer patients. Leucovorin has no effect on the pharmacokinetics of capecitabine and its metabolites. However, leucovorin has an effect on the pharmacodynamics of Intacape and its toxicity may be enhanced by leucovorin.

Sorivudine and analogues

Intacape should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. There must be at least a 4-week waiting period between the end of treatment with sorivudine or its chemically related analogues, such as brivudine and start of Intacape therapy.

Oxaliplatin

No clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occur when capecitabine and oxaliplatin were administered in combination, with or without bevacizumab.

Bevacizumab
There was no clinically significant effect of bevacizumab on the pharmacokinetic parameters of capecitabine or its metabolites.

j) Pregnancy and Lactation

Pregnancy

Pregnancy category D

There are no studies in pregnant women using Capecitabine; however, based on the pharmacological and toxicological properties of Capecitabine, it should be assumed that Capecitabine may cause fetal harm if administered to pregnant women.

Capecitabine should be considered a potential human teratogen. Intacape should not be used during pregnancy. If Intacape is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient must be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Intacape.

Nursing Mothers

It is not known whether the drug is excreted in human milk. Nursing should be discontinued during Intacape treatment.

k) Adverse Effects/ Undesirable Effects

Summary of the safety profile

The overall safety profile of capecitabine is based on data from patients treated with capecitabine as monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications. The safety profiles of capecitabine monotherapy for the metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable.

The most commonly reported and/or clinically relevant treatment-related adverse drug reactions (ADRs) were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-plantar erythrodysesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism.

Tabulated list of adverse reactions

Capecitabine monotherapy

Table 7 Summary of related ADRs reported in patients treated with capecitabine monotherapy

Body System	**Very Common** ***All grades***	**Common** ***All grades***	**Uncommon** ***Severe and/or Life-threatening (grade 3-4) or considered medically relevant***	**Rare/Very Rare (Post-Marketing Experience)**
Infections and infestations	-	Herpes viral infection, Nasopharyngitis, Lower respiratory tract infection	Sepsis, Urinary tract infection, Cellulitis, Tonsillitis, Pharyngitis, Oral candidiasis, Influenza, Gastroenteritis, Fungal infection, Infection, Tooth abscess	
Neoplasm benign, malignant and unspecified	-	-	Lipoma	
Blood and lymphatic system disorders	-	Neutropenia, Anaemia	Febrile neutropenia, Pancytopenia, Granulocytopenia, Thrombocytopenia, Leukopenia, Haemolytic anaemia, International Normalised Ratio (INR) increased/Prothrombin time prolonged	
Immune system disorders	-	-	Hypersensitivity	
Metabolism and nutrition disorders	Anorexia	Dehydration, Weight decreased	Diabetes, Hypokalaemia, Appetite disorder, Malnutrition, Hypertriglyceridaemia	
Psychiatric disorders	-	Insomnia, Depression	Confusional state, Panic attack, Depressed mood, Libido decreased	
Nervous system disorders	-	Headache, Lethargy Dizziness, Parasthesia, Dysgeusia	Aphasia, Memory impairment, Ataxia, Syncope, Balance disorder, Sensory disorder, Neuropathy peripheral	Toxic leukoencephalopathy (very rare)
Eye disorders	-	Lacrimation increased, Conjunctivitis, Eye irritation	Visual acuity reduced, Diplopia	Lacrimal duct stenosis (rare), Corneal disorders(rare), keratitis (rare), punctate keratitis (rare)
Ear and labyrinth disorders	-	-	Vertigo, Ear pain	
Cardiac disorders	-	-	Angina unstable, Angina pectoris, Myocardial ischaemia/infarction, Atrial fibrillation, Arrhythmia, Tachycardia, Sinus tachycardia, Palpitations	Ventricular fibrillation (rare), QT prolongation (rare), Torsade de pointes (rare), Bradycardia (rare), Vasospasm (rare)
Vascular disorders	-	Thrombophlebitis	Deep vein thrombosis, Hypertension, Petechiae,	

			Hypotension, Hot flush, Peripheral coldness	
Respiratory, thoracic and mediastinal disorders	-	Dyspnoea, Epistaxis, Cough, Rhinorrhoea	Pulmonary embolism, Pneumothorax, Haemoptysis, Asthma, Dyspnoea exertional	
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Stomatitis, Abdominal pain	Gastrointestinal haemorrhage, Constipation, Upper abdominal pain, Dyspepsia, Flatulence, Dry mouth	Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Abdominal pain lower, Oesophagitis, Abdominal discomfort, Gastrooesophageal reflux disease, Colitis, Blood in stool	
Hepatobiliary disorders	-	Hyperbilirubinemia, Liver function test abnormalities	Jaundice	Hepatic failure (rare), Cholestatic hepatitis (rare)
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome	Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyper-pigmentation, Rash macular, Skin desquamation, Dermatitis, Pigmentation disorder, Nail disorder	Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome	Cutaneous lupus erythematosus (rare), Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis (very rare)
Muskuloskeletal and connective tissue disorders	-	Pain in extremity, Back pain, Arthralgia	Joint swelling, Bone pain, Facial pain, Musculoskeletal stiffness, Muscular weakness	
Renal and urinary disorders	-	-	Hydronephrosis, Urinary incontinence, Haematuria, Nocturia, Blood creatinine increased	
Reproductive system and breast disorders	-	-	Vaginal haemorrhage	
General disorders and administration site conditions	Fatigue, Asthenia	Pyrexia, Oedema peripheral, Malaise, Chest pain	Oedema, Chills, Influenza like illness, Rigors, Body temperature increased	

Capecitabine in combination therapy

Table 8 Summary of related ADRs reported in patients treated with capecitabine in combination treatment **in addition to** those are seen with capecitabine monotherapy or those are seen at **a higher frequency grouping** compared to capecitabine monotherapy

Body System	**Very Common** ***All grades***	**Common** ***All grades***	**Rare/Very Rare (Post-Marketing Experience)**

Infections and infestations	-	Herpes zoster, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection , Rhinitis, Influenza, Infection, Oral herpes	
Blood and lymphatic system disorders	Neutropenia, Leucopenia, Anaemia, Neutropenic fever, Thrombocytopenia	Bone marrow depression, Febrile Neutropenia	
Immune system disorders	-	Hypersensitivity	
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia, Hyponatraemia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia	
Psychiatric disorders	-	Sleep disorder, Anxiety	
Nervous system disorders	Paraesthesia, Dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache	Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia	
Eye disorders	Lacrimation increased	Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred	
Ear and labyrinth disorders	-	Tinnitus, Hypoacusis	
Cardiac disorders	-	Atrial fibrillation, Cardiac ischaemia/infarction	
Vascular disorders	Lower limb oedema, Hypertension, Embolism and thrombosis	Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis	
Respiratory, thoracic and mediastinal system disorders	Sore throat, Dysaesthesia pharynx	Hiccups, Pharyngolaryngeal pain, Dysphonia	
Gastrointestinal disorders	Constipation, Dyspepsia	Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort	
Hepatobiliary disorders	-	Hepatic function abnormal	
Skin and subcutaneous tissue	Alopecia, Nail disorder	Hyperhidrosis, Rash erythematous, Urticaria,	

disorders		Night sweats	
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity	Pain in jaw , Muscle spasms, Trismus, Muscular weakness	
Renal and urinary disorders	-	Haematuria, Proteinuria, Creatinine renal clearance decreased, Dysuria	Acute renal failure secondary to dehydration (rare)
General disorders and administration site conditions	Pyrexia, Weakness, Lethargy, Temperature intolerance	Mucosal inflammation, Pain in limb, Pain, Chills, Chest pain, Influenza-like illness, Fever, Infusion related reaction, Injection site reaction, Infusion site pain, Injection site pain	
Injury, poisoning and procedural complications	-	Contusion	

Adverse Drug Reactions from Postmarketing Experience
Immune system disorders
Unknown: Angioedema

l) Overdose and Treatment

The manifestations of acute overdose include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

m) Storage Conditions
Do not store above 30°C.

n) Shelf Life:
24 Months

o) Dosage forms and packaging available

60 Film coated tablets
10 tablets are packed in alu-alu blister pack or PVC/PVdC-alu blister pack. Such 6blisters are packed in 1 carton.

p) Instructions for Use

Intacape tablet should be taken within 30 minutes after finishing a meal. Swallow Intacape tablets whole with water. Do not crush or cut the tablets.

q) Name and address of manufacturer/ product registration holder

Manufactured By:
INTAS PHARMACEUTICALS LIMITED.

Plot Numbers 457-458 & 191/218P,
Sarkhej-Bavla Highway,
Matoda, Sanand, Ahmedabad, Gujarat, IN-382210, India.

Product Registration Holder:
Accord Healthcare Sdn Bhd (1035160 D)
Suite 12a-15, Level 12a,
Wisma Zelan
No 1 Jalan Tasik Permaisuri 2
Bandar Tun Razak
56000 Kuala Lumpur

r) Date of revision of PI

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