

Package Insert

INTACAPE 500 mg Tablets (Capecitabine Tablets USP 500 mg)

a) Name and Strength of Active Substance

Each film coated tablet contains:
Capecitabine USP 500 mg

b) Product Description

Peach coloured, oblong shaped, biconvex, film coated tablets, debossed with '500' 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

The pharmacokinetics of capecitabine have been evaluated over a dose range of 502-3514 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 was 30%-35% higher on day 14. Capecitabine dose reduction decreases systemic exposure to 5-FU more than dose-proportionally, due to non-linear pharmacokinetics for the active metabolite.

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, but only results in a minor effect on the AUC of 5'-DFUR, and on the AUC of the subsequent metabolite 5-FU. At the dose of 1250 mg/m² on day 14 with administration after food intake, the peak plasma concentrations (C_{max} in µg/ml) for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 4.47, 3.05, 12.1, 0.95 and 5.46 respectively. The time to peak plasma concentrations (T_{max} in hours) were 1.50, 2.00, 2.00, 2.00 and 3.34. The AUC_{0-∞} values in µg•h/ml were 7.75, 7.24, 24.6, 2.03 and 36.3.

Protein binding: in vitro human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound, mainly to albumin.

Metabolism: capecitabine is first metabolised 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. Following oral administration of capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumours to adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumour to plasma was 21.4 (ranged from 3.9 to 59.9, n=8) whereas the ratio in healthy tissues to plasma was 8.9 (ranged from 3.0 to 25.8, n=8). Thymidine phosphorylase activity was measured and found to be 4 times greater in primary colorectal tumour than in adjacent normal tissue. According to immunohistochemical studies, thymidine phosphorylase 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 (FUH₂). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β -ureidopropionase 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: the elimination half-life ($t_{1/2}$ in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0.85, 1.11, 0.66, 0.76 and 3.23 respectively. 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.

Combination therapy: Phase I studies evaluating the effect of Capecitabine Tablets on the pharmacokinetics of either docetaxel or paclitaxel and vice versa showed no effect by Capecitabine Tablets on the pharmacokinetics of docetaxel or paclitaxel (C_{max} and AUC) and no effect by docetaxel or paclitaxel on the pharmacokinetics of 5'-DFUR.

Pharmacokinetics in special populations: A population pharmacokinetic analysis was carried out after Capecitabine Tablets treatment of 505 patients with colorectal cancer dosed at 1250 mg/m² twice daily. Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT had no statistically significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

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

Patients with renal impairment: Based on a pharmacokinetic study 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 (35% increase in AUC when creatinine clearance decreases by 50%) and to FBAL (114% increase in AUC when creatinine clearance decreases by 50%). FBAL is a metabolite without antiproliferative activity.

Elderly: Based on the population pharmacokinetic analysis, which included patients with a wide range of ages (27 to 86 years) and included 234 (46%) 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 (20% increase in age results in a 15% increase in the AUC of FBAL). 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/m² administered twice daily (morning and evening; equivalent to 2500 mg/m² 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/m² twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m² 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/m²/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/m² 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/m² 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/m² 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/m² twice daily continuously. Epirubicin at a dose of 50 mg/m² should be given as a bolus on day 1 every 3 weeks. The platinum based compound (cisplatin at a dose of 60 mg/m² (triple regimen) - 80 mg/m² (double regimen) or oxaliplatin at a dose of 130 mg/m²) 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.

Dose calculation

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/m² or 1000mg/m².

Table 1: Standard and reduced dose calculations according to body surface area for a starting dose of Intacape of 1250 mg/m²

	Dose level 1250 mg/m ² (twice daily)
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	Full dose 1250 mg/m ²	Reduced dose (75%) 950 mg/m ²	Reduced dose (50%) 625 mg/m ²
Body Surface Area (m ²)	Dose per administration (mg)	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1500	1150	800
1.27 - 1.38	1650	1300	800
1.39 - 1.52	1800	1450	950
1.53 - 1.66	2000	1500	1000
1.67 - 1.78	2150	1650	1000
1.79 - 1.92	2300	1800	1150
1.93 - 2.06	2500	1950	1300
2.07 - 2.18	2650	2000	1300
≥ 2.19	2800	2150	1450

Table 2: Standard and reduced dose calculations according to body surface area for a starting dose of Intacape of 1000 mg/m²

	Dose level 1000 mg/m ² (twice daily)		
	Full dose 1000 mg/m ²	Reduced dose (75%) 750 mg/m ²	Reduced dose (50%) 500 mg/m ²
Body Surface Area (m ²)	Dose per administration (mg)	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1150	800	600
1.27 - 1.38	1300	1000	600
1.39 - 1.52	1450	1100	750
1.53 - 1.66	1600	1200	800
1.67 - 1.78	1750	1300	800
1.79 - 1.92	1800	1400	900
1.93 - 2.06	2000	1500	1000
2.07 - 2.18	2150	1600	1050
≥ 2.19	2300	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 10⁹/L and/or thrombocyte counts of <100 X 10⁹/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: Intacape 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 0-1	100%
-2nd appearance		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		
-1 st 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%

-2 nd appearance	Discontinue permanently	Not applicable
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*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.

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

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

	Recommended Dose Modifications	
	Intacape 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	
1 st appearance	Interrupt until resolved (grade 0 – 1)	X: 100% of starting dose T: 100% (75mg/m ²)
2 nd appearance of same toxicity	Interrupt until resolved (grade 0 – 1)	X: 75% of starting dose T: Reduce to 55mg/m ²
3 rd appearance of same toxicity	Interrupt until resolved (grade 0 – 1)	X: 50% of starting dose T: Discontinue permanently
4 th appearance of same toxicity	Discontinue permanently	
Toxicity grade	Grade 3	
	If grade 3 haematological see section on haematological toxicity, otherwise:	
1 st appearance	Interrupt until resolved (grade 0 – 1)	X: 75% of starting dose T: Reduce to 55 mg/m ²
2 nd appearance	Interrupt until resolved (grade 0 – 1)	X: 50% of starting dose T: Discontinue permanently
3 rd appearance	Discontinue permanently	
Toxicity grade ¹	Grade 4	
	If G4 haematological see section on haematological toxicity, otherwise:	
1 st appearance	Discontinue permanently <i>or</i> (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
2 nd appearance	Discontinue permanently	

*National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-foot syndrome

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 $\geq 1.5 \times 10^9/l$ (Grade 0 - 1). Patients with neutropenia $< 0.5 \times 10^9/l$ (Grade 4) for more than 1 week, or febrile ($> 38^\circ C$) 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 $< 1.5 \times 10^9/l$ and/or thrombocyte counts of $< 1.0 \times 10^9/l$ should not be treated with the Intacape/docetaxel combination.

Hypersensitivity: Patients who develop severe hypersensitivity reactions (hypotension with a decrease of $\geq 20 \text{ mm Hg}$, 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
$\leq 1.5 \times \text{UNL}$	and $\leq 5 \times \text{UNL}$	no dose modification
$> 1.5 \times \text{UNL} - \leq 2.5 \times \text{UNL}$	and $\leq 2.5 \times \text{UNL}$	no dose modification
$> 2.5 \times \text{UNL} - \leq 5 \times \text{UNL}$	and $\leq 2.5 \times \text{UNL}$	reduce by 25% (not below 55 mg/m^2)
$> 1.5 \times \text{UNL} - \leq 5 \times \text{UNL}$	and $> 2.5 \times \text{UNL} - \leq 5 \times \text{UNL}$	reduce by 25% (not below 55 mg/m^2)
$> 5 \times \text{UNL}$	or $> 5 \times \text{UNL}$ (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	
Body surface area (m ²)	Dose per administration (mg)
≤1.26	1150
1.27 – 1.38	1300
1.39 – 1.52	1450
1.53 – 1.66	1500
1.67 – 1.78	1650
1.79 – 1.92	1800
1.93 – 2.06	1950
2.07 – 2.18	2000
≥2.19	2150

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

Dose level 625 mg/m ² twice daily	
Body surface area (m ²)	Dose per administration (mg)
≤1.38	800
1.39 – 1.52	950
1.53 – 1.66	1000
1.67 – 1.78	1000
1.79 – 1.92	1150
1.93 – 2.06	1300
2.07 – 2.18	1300
≥2.19	1450

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 [Cockcroft and Gault]) at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m² 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/m² 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/m² 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 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

Warnings

Diarrhea: Intacape can induce diarrhea, which can sometimes be severe. Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. Standard anti-diarrhea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. 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 agents. Fatal outcome of renal failure has been reported in these situations.

If Grade 2 (or higher) dehydration occurs, 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 should be applied should be applied for the precipitating adverse event as necessary.

Dihydropyrimidine dehydrogenase (DPD) deficiency: Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity, an enzyme involved in fluorouracil degradation.

Patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus that cause complete or near complete absence of DPD activity, are at the highest risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil. These patients should not be treated with Intacape. No dose has been proven safe for patients with complete absence of DPD activity.

Patients with certain heterozygous DPYD variants (eg. DPYD*2A variant) that may cause partial DPD deficiency have been shown to have increased risk of severe toxicity when treated with capecitabine. For patients with partial DPD deficiency where the benefits of Intacape 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, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity.

Testing for DPD deficiency should be considered based on the local availability and current guidelines.

In patients with unrecognised DPD deficiency treated with capecitabine as well as 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.

Precautions

The spectrum of cardiotoxicity observed with Intacape is similar to that of other fluorinated pyrimidines. This includes myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease.

Intacape can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN). Intacape should be permanently discontinued in patients who experience a severe skin reaction possibly attributable to Intacape treatment.

Intacape can induce hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema), which is a cutaneous toxicity. Persistent or severe hand-foot syndrome (grade 2 and above) can eventually lead to loss of fingerprints, which could impact patient identification. For patients receiving Intacape monotherapy in the metastatic setting, the median time to onset was 79 days (range 11 to 360 days), with a severity range of Grade 1 to 3.

Grade 1 hand-foot syndrome is defined by numbness, dysesthesia/paresthesia, tingling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 is defined as 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. If Grade 2 or 3 hand-foot syndrome occurs, administration of Intacape should be interrupted until the event resolves or decreases in intensity to Grade 1. Following Grade 3 hand-foot syndrome, subsequent doses of Intacape should be decreased. When Intacape 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 dexpantenol is effective for hand-foot syndrome prophylaxis in patients treated with Intacape.

Intacape can induce hyperbilirubinemia. Administration of Intacape should be interrupted if treatment-related elevations in bilirubin of $>3.0 \times \text{ULN}$ or treatment-related elevations in hepatic aminotransferases (ALT, AST) of $>2.5 \times \text{ULN}$ occur. Treatment may be resumed when bilirubin decreases to $\leq 3.0 \times \text{ULN}$ or hepatic aminotransferases decrease to $\leq 2.5 \times \text{ULN}$.

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

Care should be exercised when Intacape is co-administered with drugs, which are metabolized by cytochrome P450 2C9 such as for example warfarin or phenytoin. Patients receiving concomitant Intacape and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly. Patients taking phenytoin concomitantly with Intacape should be regularly monitored for increased phenytoin plasma concentrations.

General

Patients treated with Intacape should be carefully monitored for toxicity. Most ADRs are reversible and do not require permanent discontinuation of therapy, although doses may have to be withheld or reduced.

Drug Abuse and Dependence

Not applicable.

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).

Leucovorin 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

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.

Lactation

It is not known whether Intacape is excreted in human milk. No studies have been conducted to assess the impact of Intacape on milk production or its presence in human breast milk. In a study of single oral administration of Intacape to lactating mice, a significant amount of capecitabine metabolites was detected in the milk. As the potential for harm to the nursing infant is unknown, breastfeeding should be discontinued during treatment with Intacape and for 2 weeks after the final dose.

k) Adverse Effects/ Undesirable Effects

Clinical Trials

Adverse drug reactions (ADRs) considered by the investigator to be possibly, probably, or remotely related to the administration of Intacape have been obtained from clinical studies conducted with Intacape monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer), and clinical studies conducted with Intacape in combination with different chemotherapy regimens for multiple indications. ADRs are added to the appropriate category in the tables below according to the highest incidence from the pooled analysis of seven clinical trials. Within each frequency grouping ADRs are listed in descending order of seriousness. Frequencies are defined as very common $\geq 1/10$, common $\geq 5/100$ to $< 1/10$ and uncommon $\geq 1/1000$ to $< 1/100$.

Intacape monotherapy

Safety data of Intacape monotherapy were reported for patients who received adjuvant treatment for colon cancer and for patients who received treatment for metastatic breast cancer or metastatic colorectal cancer. The safety information includes data from a phase III trial in adjuvant colon cancer (995 patients treated with Intacape and 974 treated with i.v. 5-FU/LV) and from 4 phase II trials in female patients with breast cancer (N=319) and 3 trials (1 phase II and 2 phase III trials) in male and female patients with colorectal cancer (N=630). The safety profile of Intacape monotherapy is comparable in patients who received

adjuvant treatment for colon cancer and in those who received treatment for metastatic breast cancer or metastatic colorectal cancer. The intensity of ADRs was graded according to the toxicity categories of the NCIC CTC Grading System.

Table 7: Summary of ADRs reported in $\geq 5\%$ of patients treated with Intacape monotherapy

Body System ADR	Very Common ($\geq 10\%$)	Common ($\geq 5\%$ to $< 10\%$)
Metabolism and nutrition disorders	Anorexia (G3/4:1%)	Dehydration (G3/4: 3%) Appetite decreased (G3/4: $< 1\%$)
Nervous system disorders		Paraesthesia, Dysgeusia (G3/4: $< 1\%$), Headache (G3/4: $< 1\%$), Dizziness (excl. vertigo) (G3/4: $< 1\%$)
Eye disorders		Lacrimation increased Conjunctivitis (G3/4: $< 1\%$)
Gastrointestinal disorders	Diarrhea (G3/4: 13%) Vomiting (G3/4: 4%) Nausea (G3/4: 4%) Stomatitis (all)* (G3/4: 4%) Abdominal pain (G3/4: 3%)	Constipation (G3/4: $< 1\%$), Abdominal pain upper (G3/4: $< 1\%$), Dyspepsia (G3/4: $< 1\%$),
Hepatobiliary disorders		Hyperbilirubinemia (G3/4:1%)
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome ** (G3/4: 17%), Dermatitis (G3/4: $< 1\%$)	Rash, Alopecia, Erythema (G3/4:1%), Dry Skin (G3/4: $< 1\%$),
General disorders and administration site conditions	Fatigue (G3/4: 3%), Lethargy (G3/4: $< 1\%$)	Pyrexia (G3/4: $< 1\%$), Weakness (G3/4: $< 1\%$), Asthenia (G3/4: $< 1\%$)

* stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration

** Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysesthesia syndrome can eventually lead to loss of fingerprints.

Skin fissures were reported to be at least remotely related to Intacape in less than 2% of the patients in seven completed clinical trials (N= 949).

The following ADRs represent known toxicities with fluoropyrimidine therapy and were reported to be at least remotely related to Intacape in less than 5% of patients in seven completed clinical trials (N = 949):

- Gastrointestinal disorder: dry mouth, flatulence, ADRs related to inflammation/ulceration of mucous membranes such as esophagitis, gastritis, duodenitis, colitis, gastrointestinal hemorrhage.
- Cardiac disorders: edema lower limb, cardiac chest pain including angina, cardiomyopathy, myocardial ischemia/infarction, cardiac failure, sudden death, tachycardia, atrial arrhythmias including atrial fibrillation, and ventricular extrasystoles.
- Nervous system disorders: taste disturbance, insomnia, confusion, encephalopathy, and cerebellar signs such as ataxia, dysarthria, impaired balance, abnormal coordination.
- Infections and infestations: ADRs related to bone marrow depression, immune system compromise, and/or disruption of mucous membranes such as local and fatal systemic infections (including bacterial, viral, fungal etiologies) and sepsis.
- Blood and lymphatic system disorders: anemia, bone marrow depression/ pancytopenia.
- Skin and subcutaneous tissue disorders: pruritus, localized exfoliation, skin hyperpigmentation, nail disorders, photosensitivity reactions, radiation recall syndrome
- General disorders and administration site conditions: pain in limb, chest pain (non-cardiac).

- Eye: eye irritation.
- Respiratory: dyspnoea, cough
- Musculoskeletal: back pain, myalgia, arthralgia
- Psychiatric disorders: depression
- Hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing exposure. A causal relationship with Intacape treatment has not been established.

Intacape in combination therapy

Table 8 lists ADRs associated with the use of Intacape in combination therapy with different chemotherapy regimens in multiple indications and occurred in addition to those seen with monotherapy and/or at a higher frequency grouping. The safety profile was similar across all indications and combination regimens. These reactions occurred in $\geq 5\%$ of patients treated with Intacape in combination with other chemotherapies. Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin), or with bevacizumab (e.g. hypertension); however, an exacerbation by Intacape therapy cannot be excluded.

Table 8: Very common and common ADRs for Intacape in combination with different chemotherapies in addition to those seen for Intacape monotherapy

Body System Adverse Event	Very Common ($\geq 10\%$)	Common ($\geq 5\%$ to $< 10\%$)
Infections and Infestations		Infection ⁺ Oral candidiasis
Blood and lymphatic system disorders	Neutropenia ⁺ , Leukopenia ⁺ , Febrile neutropenia ⁺ , Thrombocytopenia ⁺ , Anaemia ⁺	
Metabolism and nutrition disorders	Appetite decreased	Hypokalemia, Weight Decreased
Psychiatric disorders		Insomnia
Nervous system disorders	Neuropathy peripheral, Peripheral sensory neuropathy, Neuropathy, Paraesthesia, Dysgeusia, Dysaesthesia, Headache	Hypoaesthesia
Eye disorders	Lacrimation increased	
Vascular Disorders	Thrombosis/embolism, Hypertension, Lower limb oedema	
Respiratory, thoracic and mediastinal disorders	Dysaesthesia pharynx, Sore throat	Epistaxis, Dysphonia, Rhinorrhoea, Dyspnoea
Gastrointestinal disorders	Constipation, Dyspepsia	Dry mouth
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder	

Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia, Pain in extremity	Pain in jaw, Back Pain
General disorders and administration site conditions	Pyrexia, Asthenia, Weakness, Temperature intolerance	Fever ⁺ Pain,

Frequencies based on all grades except those denoted with ⁺, which are based on G3/4 ADRs only.

Hypersensitivity reactions (2%) and cardiac ischaemia/infarction (3%) have been reported commonly for Intacape in combination with other chemotherapy but in less than 5% of patients.

Rare or uncommon ADRs reported for Intacape in combination with other chemotherapy are consistent with the ADRs reported for Intacape monotherapy or the combination product monotherapy.

Laboratory Abnormalities

The following table displays laboratory abnormalities observed in 995 patients (adjuvant colon cancer) and 949 patients (metastatic breast and colorectal cancer), regardless of relationship to treatment with Intacape.

Table 9: Laboratory abnormalities^a: Intacape monotherapy in adjuvant colon cancer and in metastatic breast and colorectal cancer

Parameter ^a	Intacape 1250 mg/m ² twice daily intermittent
	Patients with Grade 3 / 4 abnormality (%)
Increased ALAT (SGPT)	1.6
Increased ASAT (SGOT)	1.1
Increased alkaline phosphatase	3.5
Increased calcium	1.1
Decreased calcium	2.3
Decreased granulocytes	0.3
Decreased hemoglobin	3.1
Decreased lymphocytes	44.4
Decreased neutrophils	3.6
Decreased neutrophils/granulocytes	2.4
Decreased platelets	2.0
Decreased potassium	0.3
Increased serum creatinine	0.5
Decreased sodium	0.4
Increased bilirubin	20.0
Hyperglycemia	4.4

^a Laboratory abnormalities were graded according to the categories of the NCIC CTC Grading System

Postmarketing Experience

The following ADRs have been identified during post-marketing experience with Intacape based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥ 1/10); common (≥ 5/100 to < 1/10); and uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (≥ 1/1,000 to < 1/100); unknown (cannot be estimated from the available data).

Table 10: Adverse Drug Reactions from Postmarketing Experience

System Organ Class (SOC)	ADR(s)	Frequency
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Renal and urinary disorders	Acute renal failure secondary to dehydration including fatal outcome	Rare
Nervous system disorders	Toxic leukoencephalopathy	Unknown
Hepatobiliary disorders	Hepatic failure, Cholestatic hepatitis	Very rare
Metabolism and nutrition disorders	Hypertriglyceridemia	Unknown
Skin and subcutaneous tissue disorders	Cutaneous lupus erythematosus, Severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN)	Very rare
Eye disorders	Lacrimal duct stenosis NOS, Corneal disorders including keratitis	Very rare
Immune system disorders	Angioedema*	Unknown
* This subtype of hypersensitivity reaction was reported in the postmarketing setting.		

Exposure to crushed or cut Intacape tablets:

In the instance of exposure to crushed or cut Intacape tablets, the following ADRs have been reported: eye irritation, eye swelling, skin rash, headache, paresthesia, diarrhea, nausea, gastric irritation, and vomiting.

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) Ability to Drive and Use Machines

Intacape has moderate influence on the ability to drive and use machines. Patients should be advised to use caution when driving or using machines if they experience ADRs such as dizziness, fatigue, and or nausea during treatment with Intacape.

n) Storage Conditions

Do not store above 30°C.

o) Special Instructions for Use, Handling and Disposal

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

Special handling using appropriate equipment and disposal procedures, should be taken as Intacape is a cytotoxic drug. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

p) Shelf Life

36 months

q) Dosage forms and packaging available

120 Film coated tablets

10 tablets are packed in Alu-Alu blister pack. Such 12 blisters are packed in 1 carton.

r) Name and address of manufacturer/ product registration holder

Manufactured By:

Intas Pharmaceuticals Limited

Plot No-5-14, Pharmez Near Village Matoda Sarkhej-Bavla National Highway, No. 8-A
Sanand Taluka, Ahmedabad, Gujarat, 382213, India.

s) Date of revision of PI

April, 2026