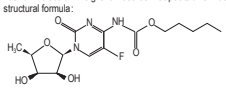
PRESCRIBING INFORMATION: For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

CAPEMAX

(CAPECITABINE TABLETS 150/500 mg)

DESCRIPTION

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl] - cytidine and has a molecular weight of 359.35. Capecitabine has the following structural formula:



COMPOSITION

CAPEMAX 150

Each film-coated tablet contains:
Capecitabine 150 mg

CAPEMAX 500

Each Film-coated tablet contains:
Capecitabine 500 mg

CLINICAL PHARMACOLOGY:

Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5-fluorouracil (5-FU) *in vivo*.

Bioactivation

Capecitabine is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.

Mechanism of Action

Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, $N^{5,10}$-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Pharmacokinetics and Drug Metabolism

Pharmacokinetics in Colorectal Tumors and Adjacent Healthy Tissue Following oral administration of capecitabine 7 days before surgery in patients with colorectal cancer, the median ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from 0.9 to 8.0). These ratios have not been evaluated in breast cancer patients or compared to 5-FU infusion.

The pharmacokinetics of capecitabine and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m^2/day. Over this range, the pharmacokinetics of capecitabine and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about ¾ of an hour. The inter-patient variability in the Cmax and AUC of 5-FU was greater than 85%.

Following oral administration of 825 mg/m^2 capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower Cmax and 24% lower AUC for capecitabine than the Caucasian patients (n=22). Japanese patients had also about 25% lower Cmax and 34% lower AUC for FBAL than the Caucasian patients. The clinical significance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

Absorption, Distribution, Metabolism and Excretion

Capecitabine reached peak blood levels in about 1.5 hours (Tmax) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of capecitabine with mean C_{max} and AUC0-∞ decreased by 60% and 35%, respectively. The C_{max} and AUC0-∞ of 5-FU were also reduced by food by 43% and 21%, respectively. Food delayed T_{max} of both parent and 5-FU by 1.5 hours.

INDICATIONS

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

Capecitabine is indicated for the treatment of metastatic colorectal cancer.

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

Capecitabine 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. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

CONTRAINDICATIONS:

- History of severe and unexpected reactions to fluoropyrimidine therapy,
- Hypersensitivity to capecitabine or to any of the excipients or fluorouracil,
- In patients with known dihydropyrimidine dehydrogenase (DPD) deficiency,
- During pregnancy and lactation,
- In patients with severe leucopenia, neutropenia, or thrombocytopenia,
- In patients with severe hepatic impairment,
- In patients with severe renal impairment (creatinine clearance below 30 ml/min),
- Treatment with sorivudine or its chemically related analogues, such as brivudine,
- If contraindications exist to any of the agents in the combination regimen, that agent should not be used.

DOSAGE AND ADMINISTRATION

Monotherapy

Colon, colorectal and breast cancer

Given as single agent, the recommended starting dose for Capecitabine in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or of locally advanced or metastatic breast cancer is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Combination therapy

Colon, colorectal and gastric cancer

In combination treatment, the recommended starting dose of Capecitabine should be reduced to 800 – 1000 mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period, or to 625 mg/m^2 twice daily when administered continuously. The inclusion of biological agents in a combination regimen has no effect on the starting dose of Capecitabine. Premedication to maintain adequate hydration and anti-emesis according to the cisplatin summary of product characteristics should be started prior to cisplatin administration for patients receiving the Capecitabine plus cisplatin combination. Premedication with antiemetics according to the oxaliplatin summary of product characteristics is recommended for patients receiving the Capecitabine plus oxaliplatin combination.

Adjuvant treatment in patients with stage III colon cancer is recommended for duration of 6 months.

Breast cancer

In combination with docetaxel, the recommended starting dose of Capecitabine in the treatment of metastatic breast cancer is 1250 mg/m^2 twice daily for 14 days 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 with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started prior to docetaxel administration for patients receiving the Capecitabine plus docetaxel combination.

Capecitabine Dose Calculations

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

	Dose level 1250 mg/m^2 (twice daily)					
	Full dose 1250 mg/m^2	Number of 150 mg tablets, 300 mg tablets and/or 500 mg 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	300 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	-	1	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	-	1	4	1800	1150
1.93-2.06	2500	-	-	5	1950	1300
2.07-2.18	2650	1	-	5	2000	1300
≥ 2.19	2800	-	1	5	2150	1450

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

	Dose level 1000 mg/m^2 (twice daily)					
	Full dose 1000 mg/m^2	Number of 150 mg tablets, 300 mg tablets and/or 500 mg 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 Surface Area (m^2)	Dose per administration (mg)	150 mg	300 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1150	1	-	2	800	600
1.27-1.38	1300	-	1	2	1000	600
1.39-1.52	1450	1	1	2	1100	750
1.53-1.66	1600	-	2	2	1200	800
1.67-1.78	1750	1	-	3	1300	800
1.79-1.92	1800	-	1	3	1400	900
1.93-2.06	2000	-	-	4	1500	1000
2.07-2.18	2150	1	-	4	1600	1050
≥ 2.19	2300	-	1	4	1750	1100

Dose adjustments during treatment:

General

Toxicity due to Capecitabine administration may be managed by symptomatic treatment and/or modification of the 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, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption. Patients taking Capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of Capecitabine omitted for toxicity are not replaced. The following are the recommended dose modifications for toxicity:

Table 3 Capecitabine Dose Reduction Schedule (3-weekly Cycle or Continuous Treatment)

Toxicity 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*		
-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 hyperbilirubinaemia.

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 Capecitabine. If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below 1.0 x 10^9/L or that the platelet count drops below 75 x 10^9/L, treatment with Capecitabine should be interrupted.

Dose modifications for toxicity when Capecitabine is used as a 3 weekly cycle in combination with other agents:

Dose modifications for toxicity when Capecitabine is used as a 3 weekly cycle in combination with other agents should be made according to Table 3 above for Capecitabine and according to the appropriate summary of product characteristics for the other medical product(s)

At the beginning of a treatment cycle, if a treatment delay is indicated for either Capecitabine or the other agent(s), and then administration of all agents should be delayed until the requirements for restarting all drugs are met.

During a treatment cycle for those toxicities considered by the treating physician not to be related to Capecitabine, Capecitabine should be continued and the dose of the other agent should be adjusted according to the appropriate Prescribing Information.

If the other agent(s) have to be discontinued permanently, Capecitabine treatment can be resumed when the requirements for restarting Capecitabine are met.

This advice is applicable to all indications and to all special populations.

Dose modifications for toxicity when Capecitabine is used continuously in combination with other agents:

Dose modifications for toxicity when Capecitabine is used continuously in combination with other agents should be made according to Table 3 above for Capecitabine and according to the appropriate summary of product characteristics for the other medical product(s).

Dose adjustments for special populations:

Hepatic impairment: insufficient safety and efficacy data are available in patients with hepatic impairment to provide a dose adjustment recommendation. No information is available on hepatic impairment due to cirrhosis or hepatitis.

Renal impairment: Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min [Cockcroft and Gault] at baseline). The incidence of grade 3 or 4 adverse reactions in patients with moderate renal impairment (creatinine clearance 30-50 ml/min at baseline) is increased compared to the overall population. In patients with moderate renal impairment at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m^2 is recommended. In patients with moderate renal impairment at baseline, no dose reduction is required for a starting dose of 1000 mg/m^2. In patients with mild renal impairment (creatinine clearance 51-80 ml/min at baseline) no adjustment of the starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3 or 4 adverse events during treatment and subsequent dose adjustment as outlined in Table 3 above. If the calculated creatinine clearance decreases during treatment to a value below 30 ml/min, Capecitabine should be discontinued. These dose adjustment recommendations for renal impairment apply both to monotherapy and combination use.

There is no experience in children (under 18 years).

Elderly:

During Capecitabine monotherapy, no adjustment of the starting dose is needed. However, grade 3 or 4 treatment-related adverse reactions were more frequent in patients 60 years of age compared to younger patients.

When Capecitabine was used in combination with other agents, elderly patients (65 years) experienced more grade 3 and grade 4 adverse drug reactions, including those leading to discontinuation, compared to younger patients. Careful monitoring of patients 60 years of age is advisable.

In combination with docetaxel: an increased incidence of grade 3 or 4 treatment-related adverse reactions and treatment-related serious adverse reactions were observed in patients 60 years of age or more. For patients 60 years of age or more, a starting dose reduction of Capecitabine to 75% (950 mg/m2 twice daily) is recommended. If no toxicity is observed in patients 60 years of age treated with a reduced Capecitabine starting dose in combination with docetaxel, the dose of Capecitabine may be cautiously escalated to 1250 mg/m^2 twice daily.

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

SIDE EFFECTS

The most common side effects of capecitabine are:

Diarrhea, nausea, vomiting, sores in the mouth and throat (stomatitis), stomach area pain (abdominal pain), upset stomach, constipation, loss of appetite, and too much water loss from the body (dehydration). These side effects are more common in patients age 80 and older.

Hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, and hair loss.

Tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and muscle pain), trouble sleeping, and taste problems.

These side effects may differ when taking capecitabine with Taxotere. Please consult your doctor for possible side effects that may be caused by taking capecitabine with Taxotere. If you are concerned about these or any other side effects while taking capecitabine, talk to your doctor.

Very Rarely Severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis has been observed.

Stop taking capecitabine immediately and contact your doctor right away if you have the side effects listed below, or other side effects that concern you.

Your doctor can then adjust capecitabine to a dose that is right for you or stop your capecitabine treatment for a while. This should help to reduce the side effects and stop them from getting worse

Diarrhea: if you have an additional 4 bowel movements each day beyond what is normal or any diarrhea at night.

Vomiting: if you vomit more than once in a 24-hour time period.

Nausea: if you lose your appetite, and the amount of food you eat each day is much less than usual.

Stomatitis: if you have pain, redness, swelling or sores in your mouth.

Hand-and-Foot Syndrome: if you have pain, swelling or redness of your hands or feet that prevents normal activity.

Fever or Infection: if you have a temperature of 100.5°F or greater, or other signs of infection.

Your doctor may tell you to lower the dose or to stop capecitabine treatment for a while. If caught early, most of these side effects usually improve after you stop taking capecitabine. If they do not improve within 2 to 3 days, call your doctor again. After your side effects have improved, your doctor will tell you whether to start taking capecitabine again and what dose to take. Adjusting the dose of capecitabine to be right for each patient is an important part of treatment.

DRUG INTERACTIONS

Drug-Drug Interactions

Anticoagulants

In four patients with cancer, chronic administration of capecitabine (1250 mg/m^2 bid) with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8-fold, and the maximum observed mean INR value was increased by 91%.

Drugs Metabolized by Cytochrome P450 Enzymes

In vitro enzymatic studies with human liver microsomes indicated that capecitabine and its metabolites (5'-DFUR, 5'-DFCR, 5-FU, and FBAL) had no inhibitory effects on substrates of cytochrome P450 for the major isoenzymes such as 1A2, 2A6, 3A4, 2C9, 2C19, 2D6, and 2E1.

Antacid

When Maalox® (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after capecitabine (1250 mg/m^2, n=12 cancer patients), AUC and C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of Capecitabine.

Capecitabine has a low potential for pharmacokinetic interactions related to plasma protein binding.

Drug-Food Interaction

In all clinical trials, patients were instructed to administer capecitabine within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered with food.

WARNINGS:

Special warnings and precautions for use

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. 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 applied should be applied for the precipitating adverse event as necessary.

Hand-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. 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 handfoot 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.

Cardiotoxicity. Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These adverse reactions may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias, 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 disturbance- Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during Capecitabine treatment.

Coumarin-derivative anticoagulation- In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC (+57%) of S-warfarin. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. 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.

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.

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.

OVERDOSE:

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.

Single doses of Capecitabine Tablets were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg

List of Excipients:

Anhydrous Lactose, Microcrystalline Cellulose, Crosscarmellose Sodium, Hypromellose E-5, Magnesium Stearate, hypromellose 6cps, Talc, Titanium Dioxide, Ferric Oxide red, Ferric Oxide Yellow, Purified water

PACKAGING AND STORAGE:

Do not store above 30°C.

Keep out of the reach and sight of children.

The Alu-Alu blister pack of 10 tablets.

Such 03 blisters are packed in carton along with leaflet.

Such 12 blisters are packed in carton along with leaflet.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.

Plot No.: 457 &458, Village Matoda,
Bavla Road and Plot No.191/218 P, Village Chacharwadi,
Tal-Sanand, Vill: Matoda & Chacharwadi, 382 210,
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