

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Teysuno 15 mg/4.35 mg/11.8 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 15 mg tegafur, 4.35 mg gimeracil and 11.8 mg oteracil (as 14.7 mg of oteracil monopotassium).

Excipient(s)

Each hard capsule contains 70.2 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The capsule has an opaque white body and opaque brown cap imprinted "TC448" in grey.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin (see section 5.1).

4.2 Posology and method of administration

Teysuno should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products.

Posology

The recommended standard dose of Teysuno when administered in combination with cisplatin is 25 mg/m² (expressed as tegafur content) twice daily, morning and evening, for 21 consecutive days followed by 7 days rest (1 treatment cycle). This treatment cycle is repeated every 4 weeks.

The standard and reduced Teysuno and cisplatin doses and calculations according to body surface area (BSA) for doses of Teysuno given in combination with cisplatin are provided in Table 1 and Table 2, respectively. The patient's BSA must be recalculated and the Teysuno dose adjusted accordingly if a patient's weight increases or decreases by $\geq 10\%$ from the one used for the previous calculation of BSA and the change is clearly not related to fluid retention.

The recommended dose of cisplatin with this regimen is 75 mg/m² by intravenous infusion administered once every 4 weeks. Cisplatin should be discontinued after 6 cycles without withdrawal of Teysuno. If cisplatin is discontinued before 6 cycles, Teysuno treatment alone can be resumed when the criteria for restarting it are met.

Patients treated with Teysuno in combination with cisplatin should be closely monitored and laboratory tests, including haematology, liver function, renal function, and serum electrolytes, should be performed frequently. Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

Refer to the cisplatin summary of product characteristics (SmPC) for pretreatment hyperhydration.

Patients should be provided with outpatient prescriptions for anti-emetic and anti-diarrhoeal medicinal products.

Teysuno doses

Table 1: Standard dose and dose reductions allowed for Teysuno and/or for cisplatin

Medicinal product	Standard dose (mg/m ²)		Dose reduction 1 (mg/m ²)		Dose reduction 2 (mg/m ²)
Teysuno	25 ^a	→	20 ^a	→	15 ^a
and/or					
Cisplatin	75	→	60	→	45

^a Expressed as tegafur content.

Teysuno dose calculations

Table 2: Standard and reduced dose calculations by body surface area (m²)

Teysuno dose	Each dose in mg (each dosing) ^a	Total daily dose in mg ^a	Number of capsules for each dose (2 doses/day)	
			15 mg capsule ^a (brown/white)	20 mg capsule ^a (white)
Standard dose^a: 25 mg/m²				
BSA ≥ 2.30 m ²	60	120	0	3
BSA = 2.10 - 2.29 m ²	55	110	1	2
BSA = 1.90 - 2.09 m ²	50	100	2	1
BSA = 1.70 - 1.89 m ²	45	90	3	0
BSA = 1.50 - 1.69 m ²	40	80	0	2
BSA = 1.30 - 1.49 m ²	35	70	1	1
BSA ≤ 1.29 m ²	30	60	2	0
First dose reduction^a: to 20 mg/m²				
BSA ≥ 2.13 m ²	45	90	3	0
BSA = 1.88 - 2.12 m ²	40	80	0	2
BSA = 1.63 - 1.87 m ²	35	70	1	1
BSA = 1.30 - 1.62 m ²	30	60	2	0
BSA ≤ 1.29 m ²	20	40	0	1
Second dose reduction^a: to 15 mg/m²				
BSA ≥ 2.17 m ²	35	70	1	1
BSA = 1.67 - 2.16 m ²	30	60	2	0
BSA = 1.30 - 1.66 m ²	20	40	0	1
BSA ≤ 1.29 m ²	15	30	1	0

Calculate BSA to 2 decimal places.
^a Expressed as tegafur content.

Adjustments during treatment

General

Toxicity due to Teysuno administration should be managed with symptomatic treatment and/or treatment interruption or dose reduction. Patients taking Teysuno should be informed of the risks and instructed to contact their physician immediately if moderate or severe toxicity occurs.

Doses omitted for toxicity are not replaced; and, if a patient vomits after taking a dose, this dose should not be replaced.

Once the Teysuno dose has been reduced, it should not be increased again.

Teysuno dose modification criteria

Dose modifications for toxicity should be made according to Tables 1, 3, 4, and 5. A maximum of two consecutive dose reductions for each medicinal product, as described in Table 1, can be applied in case of toxicity. Each dose reduction results in approximately 20-25% reduction of dose. See Table 2 for the details of the number of Teysuno capsules to be administered for each dose level. For minimum criteria for resumption of Teysuno treatment, see Table 6.

Teysuno dose modifications for toxicity when used in combination with cisplatin can be made in two ways.

- *During a 4-week cycle of treatment*

Teysuno should only be given on Days 1 to 21 of each cycle, i.e., treatment should not be given on Days 22 to 28 of a cycle. Treatment days missed in a cycle where drug was held due to toxicity should not be replaced.

During a treatment cycle, dose adjustment should be performed for each individual medicinal product that is considered to be causally related to the toxicity, if such a distinction can be made. If both medicinal products are considered to be causing the toxicity or it is not possible to distinguish them, then dose reduction should be performed for both according to the recommended dose reduction schedule.

- *At the initiation of subsequent cycles of treatment*

If a treatment delay is indicated for either Teysuno or cisplatin, then administration of both medicinal products should be delayed until the requirements for restarting both are met unless one of the medicinal products has been permanently discontinued.

Dose modifications for Teysuno for adverse reactions in general except for haematologic and renal toxicities

Table 3: Teysuno dose reduction schedule for treatment-related toxicities in general, except for haematologic and renal toxicities

Toxicity grades ^a	Teysono dose changes within a 21-day treatment cycle	Teysono dose adjustment for next dose / next cycle
Grade 1		
Any occurrence	Maintain treatment at same dose level	None
Grade 2^{b,c}		
Any occurrence	Suspend treatment until Grade 0 or 1	None
Grade 3 or Higher^c		
First occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from previous level
Second occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from previous level
Third occurrence	Discontinue treatment	Discontinue treatment
^a According to the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. ^b For Grade 2 nausea and/or vomiting, the anti-emetic therapy should be optimized prior to a suspension of Teysuno. ^c At the discretion of the treating physician, patients may continue with treatment without reduction or interruption for adverse reactions (irrespective of grade) considered unlikely to become serious or life-threatening (e.g., alopecia, changes in sexual function, and dry skin).		

Dose modifications for renal toxicities

Creatinine clearance (CrCl) must be determined for every cycle before the start of treatment on Day 1.

Table 4: Teysuno and cisplatin dose modification according to creatinine clearance values at the start of a cycle of treatment

Creatinine clearance	Teysono dose modification at the start of the cycle of treatment	Cisplatin dose modification at the start of the cycle of treatment
≥50 ml/min	No dose modification	No dose modification
30 to 49 ml/min	Start treatment at one reduced dose level	Start cisplatin treatment at a 50% dose reduction from the previous cycle
≤30 ml/min	Suspend treatment until resumption criterion (≥30 ml/min) is met and then start treatment at one reduced dose level	Suspend cisplatin treatment until resumption criterion (≥30 ml/min) is met and then start treatment at a 50% dose reduction from the previous cycle

Dose modifications for haematologic toxicities

Table 5: Haematologic toxicities for which Teysuno treatment should be suspended

Units	Neutrophils	Platelets	Haemoglobin	Teysono dose modification
IU	<0.5 x 10 ⁹ /l	<25 x 10 ⁹ /l	4.0 mmol/l	Suspend treatment until resumption criterion is met (see Table 6) and then resume dosing at one reduced dose level.

Resumption criteria for Teysuno treatment

Table 6: Minimum criteria to resume Teysuno treatment following its suspension due to a toxicity

Non-haematologic	Haematologic
Baseline or Grade 1	Platelet count $\geq 100 \times 10^9/l$
Calculated creatinine clearance ≥ 30 ml/min	Neutrophils $\geq 1.5 \times 10^9/l$
	Haemoglobin ≥ 6.2 mmol/l
CrCl must be calculated at the beginning of every cycle before the start of treatment with Teysuno on Day 1.	

Dose modifications for special populations

Renal impairment

- Mild renal impairment (CrCl 51 to 80 ml/min)

No adjustment of the standard dose is recommended in patients with mild renal impairment (see section 5.2).

- Moderate renal impairment (CrCl 30 to 50 ml/min)

The recommended standard dose in patients with moderate renal impairment is 20 mg/m² twice daily (expressed as tegafur content) (see sections 4.8 and 5.2).

- Severe renal impairment (CrCl below 30 ml/min)

Use is contraindicated in severe renal impairment (see sections 4.3 and 4.4).

Elderly

No adjustment of the standard dose is recommended in patients ≥ 70 years old (see section 4.8).

Hepatic impairment

No adjustment of the standard dose is recommended for patients with hepatic impairment (see section 5.2).

Ethnicity

No adjustment of the standard dose is recommended for patients of Asian ethnicity (see section 5.2).

Paediatric population

The safety and efficacy of Teysuno in children and adolescents under 18 years old have not been established. No data are available. Therefore, Teysuno should not be administered to children or adolescents under 18 years of age.

Method of administration

Capsules should be taken by mouth with water at least 1 hour before or 1 hour after a meal (see section 5.2).

4.3 Contraindications

- Hypersensitivity to any of the active substances (tegafur, gimeracil, and oteracil) or to any of the excipients (see sections 4.4 and 6.1).
- History of severe and unexpected reactions to fluoropyrimidine therapy.
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Pregnancy and breastfeeding.
- Severe bone marrow suppression (severe leukopaenia, neutropaenia, or thrombocytopaenia; see section 4.2, Table 5).
- Severe renal impairment (CrCl below 30 ml/min).
- Co-administration of other fluoropyrimidines with Teysuno.
- Treatment within 4 weeks with DPD inhibitors, including sorivudine or its chemically related analogues such as brivudine.
- Contraindications for cisplatin; refer to the cisplatin SmPC.

4.4 Special warnings and precautions for use

Dose limiting toxicities include diarrhoea and dehydration. Most adverse reactions are reversible and can be managed by symptomatic therapy, dose interruptions and dose reductions.

Bone marrow suppression

Treatment-related bone marrow suppression, including neutropaenia, leukopaenia, thrombocytopaenia, anaemia, and pancytopaenia, has been reported among patients treated with Teysuno in combination with cisplatin. Patients with low white blood cell counts should be monitored carefully for infection and risk of other complications of neutropaenia and treated as medically indicated (e.g., with antibiotics, granulocyte-colony stimulating factor [G-CSF]). Patients with low platelet counts are at increased risk for bleeding and should be monitored carefully. The dose should be modified as recommended in section 4.2.

Diarrhoea

Patients with diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Prophylactic treatment for diarrhoea should be administered as indicated. Standard anti-diarrhoeal therapy (e.g., loperamide) and intravenous fluids/electrolytes should be initiated early when diarrhoea develops. Dose suspension/adjustment should be implemented with the occurrence of Grade 2 or higher diarrhoea if symptoms persist despite adequate treatment.

Dehydration

Dehydration and any associated electrolyte disturbances should be prevented or corrected at onset. Patients with anorexia, asthenia, nausea, vomiting, diarrhoea, stomatitis, and gastrointestinal obstruction should be monitored closely for signs of dehydration. Dehydration should be managed aggressively with rehydration and other appropriate measures. If Grade 2 (or higher) dehydration occurs, treatment should be immediately suspended and the dehydration corrected. Treatment should not be resumed until dehydration and its underlying causes are corrected or adequately controlled. Dose modifications should be applied for the precipitating adverse reaction as necessary (see section 4.2).

Renal toxicity

Treatment with Teysuno in combination with cisplatin may be associated with a transient decline of glomerular filtration rate caused primarily by pre-renal factors (e.g., dehydration, electrolyte imbalance, etc). Adverse reactions of Grade 3 or higher such as increased blood creatinine, decreased creatinine clearance, toxic nephropathy, and acute renal failure have all been reported in patients receiving Teysuno in combination with cisplatin (see section 4.8). To detect early changes in renal function during treatment, renal parameters should be closely monitored (e.g., serum creatinine, CrCl). If deterioration of glomerular filtration rate is observed, Teysuno and/or cisplatin dose should be adjusted according to Table 4, and appropriate supportive measures taken (see section 4.2).

Dehydration and diarrhoea may increase the risk of renal toxicity for cisplatin. Hyperhydration (forced diuresis) should be administered according to the cisplatin SmPC to reduce the risk of renal toxicity associated with cisplatin therapy.

Gimeracil increases 5-fluorouracil (5-FU) exposure by inhibiting DPD, the primary enzyme for metabolizing 5-FU. Gimeracil is primarily cleared by the kidney (see section 5.2); so, in patients with renal insufficiency gimeracil renal clearance is decreased and 5-FU exposure thus increased. Treatment-related toxicities can be expected to increase as 5-FU exposure increases (see section 5.2).

Ocular toxicity

The most common treatment-related ocular disorders among patients in studies in Europe/United States of America (EU/USA) treated with Teysuno in combination with cisplatin were lacrimal disorders (8.8%), including increased lacrimation, dry eye, and acquired dacryostenosis (see section 4.8).

Most ocular reactions will resolve or improve with suspension of medicinal product and proper treatment (instillation of artificial tears, antibiotic eye drops, implantation of glass or silicone tubes in lacrimal punctas or canaliculi, and/or use of spectacles rather than contact lenses). Efforts should be made to ensure early detection of ocular reactions, including an early ophthalmologic consultation in the event of any persistent or vision-reducing ocular symptoms such as lacrimation or corneal symptoms.

Refer to the cisplatin SmPC for eye disorders observed with cisplatin therapy.

Coumarin-derivative anticoagulant

Patients receiving oral coumarin-derivative anticoagulant therapy must have their anticoagulant response (International Normalized Ratio for prothrombin time [INR] or prothrombin time [PT]) monitored closely and the anticoagulant dose adjusted accordingly (see section 4.5). The use of coumarin-derivative anticoagulant in clinical trials has been associated with elevated INR and gastrointestinal bleeding, bleeding tendency, haematuria, and anaemia in patients receiving Teysuno therapy.

DPD inducers

If a DPD inducer were to be concomitantly administered with Teysuno, the exposure of 5-FU might not reach the efficacious level. However, since no DPD inducers are currently known, the interaction between a DPD inducer and Teysuno can not be evaluated.

Microsatellite instability (MSI)

Teysuno has not been studied in gastric cancer patients with MSI. The association between 5-FU sensitivity and MSI in patients with gastric cancer is unclear and the association between Teysuno and MSI in gastric cancer is unknown.

Glucose/galactose intolerance/malabsorption

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose/galactose malabsorption should not take this medicinal product.

Other oral fluoropyrimidines

No clinical trials are available comparing Teysuno versus other oral 5-FU compounds. Therefore, Teysuno cannot be used as a substitute for other oral 5-FU products.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products

No interaction studies have been performed in adult or paediatric patients.

Other fluoropyrimidines

Co-administration of other fluoropyrimidines such as capecitabine, 5-FU, tegafur, or flucytosine can lead to additive toxicities, and is contraindicated. A minimum washout period of 7 days is recommended between administration of Teysuno and other fluoropyrimidines. The washout period described in the SmPC of other fluoropyrimidine medicinal products should be followed if Teysuno is to be administered subsequent to other fluoropyrimidine medicinal products.

Sorivudine and brivudine

Sorivudine or its chemically related analogues such as brivudine irreversibly inhibit DPD, resulting in a significant increase in 5-FU exposure. This may lead to increased clinically significant fluoropyrimidine-related toxicities with potentially fatal outcomes. Teysuno must not be used with sorivudine or brivudine or within 4 weeks of the last dose of sorivudine or brivudine.

CYP2A6 inhibitors

As CYP2A6 is the major enzyme responsible for the conversion of tegafur to 5-FU, co-administration of a known CYP2A6 inhibitor and Teysuno should be avoided as effectiveness of Teysuno could be decreased (see section 5.2).

Folate/folinic acid

No data are available on the concomitant use of folinic acid with Teysuno in combination with cisplatin. However, metabolites of folinate/folinic acid will form a ternary structure with thymidylate

synthase and fluorodeoxyuridine monophosphate (FdUMP), potentially increasing the cytotoxicity of 5-FU. Caution is advised as folinic acid is known to enhance the activity of 5-FU.

Nitroimidazoles, including metronidazole and misonidazole

No data are available on the concomitant use of nitroimidazoles with Teysuno in combination with cisplatin. However, nitroimidazoles may reduce clearance of 5-FU and thus increase plasma levels of 5-FU. Caution is advised as co-administration may increase the toxicity of Teysuno.

Methotrexate

No data are available on the concomitant use of methotrexate with Teysuno in combination with cisplatin. However, polyglutamated methotrexate inhibits thymidylate synthase and dihydrofolate reductase, potentially increasing cytotoxicity of 5-FU. Caution is advised as co-administration may increase the toxicity of Teysuno.

Clozapine

No data are available on the concomitant use of clozapine with Teysuno in combination with cisplatin. However, due to possible additive pharmacodynamic effects (myelotoxicity), caution is advised as co-administration may increase the risk and severity of haematologic toxicity of Teysuno.

Cimetidine

No data are available on the concomitant use of cimetidine with Teysuno in combination with cisplatin. However, co-administration may decrease clearance and, thus increase plasma levels of 5-FU. Caution is advised as co-administration may increase the toxicity of Teysuno.

Coumarin-derivative anticoagulant

The activity of a coumarin-derivative anticoagulant was enhanced by Teysuno. Caution is advised as co-administration of Teysuno and coumarin anticoagulation therapy may increase the risk of bleeding (see section 4.4).

Phenytoin

Fluoropyrimidines may increase phenytoin plasma concentration when administered concomitantly with phenytoin causing phenytoin toxicity. Frequent monitoring of phenytoin blood/plasma levels is advised when Teysuno and phenytoin are administered concomitantly. If indicated, the dose of phenytoin should be adjusted according to the phenytoin SmPC. If phenytoin toxicity develops, appropriate measures should be taken.

Other

Based on non-clinical data, allopurinol may decrease anti-tumour activity due to suppression of phosphorylation of 5-FU. Therefore, concurrent administration with Teysuno should be avoided.

Other forms of interaction

Food

Administration of Teysuno with a meal reduced exposure to oteracil and gimeracil, with a more pronounced effect for oteracil than for gimeracil (see section 5.2). It should be taken with water at least 1 hour before or 1 hour after a meal (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with this medicinal product.

Contraception in males and females

Contraceptive measures must be taken by both male and female patients during and up to 6 months after stopping treatment with Teysuno.

Pregnancy

Teysuno is contraindicated in pregnancy (see section 4.3). There are no data from the use of Teysuno in pregnant women. Studies in animals have shown reproductive toxicity. As with other fluoropyrimidines, Teysuno administration caused embryoletality and teratogenicity in animals (see section 5.3). If the patient becomes pregnant while receiving Teysuno, treatment should be discontinued and the potential risk to the foetus must be explained. Genetic counseling should be considered.

Breastfeeding

Teysuno is contraindicated during breastfeeding (see section 4.3). It is not known whether Teysuno or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of Teysuno or its metabolites in milk (for details see section 5.3).

A risk to newborns/infants cannot be excluded. Breastfeeding should be discontinued while receiving treatment with Teysuno.

Fertility

No data are available on the effect of Teysuno in combination with cisplatin on human fertility. Non-clinical studies demonstrated that Teysuno did not appear to affect male or female fertility in the rat (see section 5.3).

Refer to the cisplatin SmPC for the effects of cisplatin on fertility, pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Teysuno has a moderate influence on the ability to drive and use machines as fatigue, dizziness, blurred vision, and nausea are common adverse reactions of Teysuno in combination with cisplatin.

4.8 Undesirable effects

Summary of safety profile

The overall safety profile of Teysuno in combination with cisplatin is based primarily on clinical study data from 593 patients with advanced gastric cancer treated with this regimen. In addition, there is post-marketing experience in over 866,000 Asian (mainly Japanese) patients.

Among 593 patients treated with Teysuno in combination with cisplatin, the most common severe adverse reactions (Grade 3 or higher with frequency of at least 10%) were neutropaenia, anaemia, and fatigue.

List of adverse reactions

The following headings are used to rank the adverse reactions by frequency: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available data). The frequencies of very common, common, and uncommon adverse reactions are from 593 patients treated with Teysuno in combination with cisplatin in clinical trials. The frequencies of medically relevant rare and very rare adverse reactions are estimated from post-marketing surveillance of 866,000 patients in Asia (mostly Japanese) treated with Teysuno-based therapy. Each term is presented in its most common category only and within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 7: Adverse reactions reported by decreasing seriousness in each frequency grouping

System Organ Class ^a	Very Common	Common	Uncommon	Rare / Very Rare
Infections and Infestations			Neutropenic sepsis, septic shock, sepsis, infection, pneumonia, bacteremia, respiratory tract infection, upper respiratory tract infection, pyelonephritis acute, urinary tract infection, pharyngitis, nasopharyngitis, rhinitis, tooth infection, candidiasis, oral herpes, paronychia, furuncle	
Neoplasms Benign, Malignant and Unspecified (Incl. cysts and polyps)			Tumour haemorrhage, cancer pain	
Blood and Lymphatic System Disorders	Neutropenia, leukopenia, anaemia, thrombocytopenia	Febrile neutropenia, lymphopenia	Pancytopenia, prothrombin time prolonged, international normalised ratio increased, hypoprothrombinaemia, prothrombin time shortened, granulocytosis, leukocytosis, eosinophilia, lymphocytosis, monocyte count decreased, monocyte count increased, thrombocythaemia	Disseminated intravascular coagulation
Immune System Disorders			Hypersensitivity	
Endocrine Disorders			Adrenal haemorrhage	
Metabolism and Nutrition Disorders	Anorexia	Dehydration, hypokalaemia, hyponatraemia, hypocalcaemia, hypomagnesaemia, hypoalbuminaemia, hyperkalaemia	Hyperglycaemia, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, hypophosphatemia, hypermagnesaemia, gout, hypoproteinaemia, hyperglobulinaemia, hyperlipidaemia, oral intake reduced	
Psychiatric Disorders		Insomnia	Confusional state, restlessness, personality disorder, hallucination, depression, anxiety, libido decreased, sexual inhibition	
Nervous System Disorders	Peripheral neuropathy	Dizziness, headache, dysgeusia	Cerebrovascular accident, cerebellar infarction, cerebrovascular disorder, convulsion, ischaemic stroke, syncope, hemiparesis, aphasia, ataxia, metabolic encephalopathy, loss of consciousness, acoustic neuritis, memory impairment, balance disorder, somnolence, tremor, ageusia, parosmia, burning sensation, formication	Leukoencephalopathy, anosmia
Eye Disorders		Vision disorder, lacrimal disorder, conjunctivitis, eye disorder	Eye allergy, eyelid ptosis, erythema of eyelid	Corneal erosion, corneal disorder

System Organ Class ^a	Very Common	Common	Uncommon	Rare / Very Rare
Ear and Labyrinth Disorders		Hearing impairment, deafness	Vertigo, ear congestion, ear discomfort	
Cardiac Disorders			Cardiac failure, acute myocardial infarction, pericardial effusion, atrial fibrillation, angina pectoris, cardiac fibrillation, tachycardia, palpitations	
Vascular Disorders		Hypotension, deep vein thrombosis, hypertension	Iliac artery thrombosis, hypovolaemic shock, arterial limb thrombosis, thrombosis, flushing, pelvic venous thrombosis, thrombophlebitis, phlebitis, phlebitis superficial, orthostatic hypotension, haematoma, hyperaemia, hot flush	
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea, epistaxis, hiccups, cough	Pulmonary embolism, respiratory tract haemorrhage, exertional dyspnoea, pharyngolaryngeal pain, rhinorrhoea, pharyngeal erythema, rhinitis allergic, dysphonia, productive cough, nasal congestion	Interstitial lung disease
Gastrointestinal Disorders	Diarrhoea, vomiting, nausea, constipation	Gastrointestinal haemorrhage, stomatitis, gastrointestinal inflammation, flatulence, abdominal pain, dysphagia, abdominal discomfort, dyspepsia, dry mouth	Gastrointestinal perforation, oesophagitis, gastrointestinal infection, ileus, gastrointestinal obstruction, ascites, lip oedema, oesophageal spasm, gastric ulcer, gastroesophageal reflux disease, reflux gastritis, retroperitoneal fibrosis, gastrointestinal disorder, anal haemorrhage, haemorrhoids, salivary hypersecretion, retching, salivary gland disorder, cheilitis, aerophagia, eructation, glossodynia, oral pain, teeth brittle	Acute pancreatitis
Hepatobiliary Disorders		Hyperbilirubinaemia, alanine aminotransferase increased, aspartate aminotransferase increased	Liver function test abnormal, gamma glutamyltransferase increased	Acute hepatic failure
Skin and Subcutaneous Tissue Disorders		Palmar-plantar erythrodysesthesia syndrome, rash, skin hyperpigmentation, dry skin, pruritus, alopecia,	Exfoliative rash, skin exfoliation, necrolytic migratory erythema, blood blister, dermatitis allergic, skin reaction, dermatitis acneiform, erythema, increased tendency to bruise, purpura, hyperhidrosis, night sweats, nail atrophy, pigmentation disorder, skin discoloration, hypertrichosis	Toxic epidermal necrolysis, Stevens-Johnson syndrome, photosensitivity reaction, nail disorder
Musculoskeletal and Connective Tissue Disorders		Musculoskeletal pain	Muscle spasms, arthralgia, pain in extremity, back pain, neck pain, bone pain, joint swelling, limb discomfort, muscle tightness, muscular weakness	Rhabdomyolysis
Renal and Urinary Disorders		Renal failure, blood creatinine increased, glomerular filtration rate decreased, blood urea increased	Toxic nephropathy, oligouria, haematuria, renal impairment, pollakiuria, blood creatine increased, blood creatinine decreased	
Reproductive System and Breast Disorders			Erectile dysfunction, breast tenderness, nipple pain	
General Disorders and Administration Site Conditions	Fatigue, asthenia	Mucosal inflammation, pyrexia, weight decreased, peripheral oedema, chills	Multi-organ failure, performance status decreased, pain, oedema, chest pain, chest discomfort, generalized oedema, face oedema, local swelling, localized oedema, weight increased, early satiety, feeling cold, injection site reaction, malaise	

System Organ Class ^a	Very Common	Common	Uncommon	Rare / Very Rare
Injury, Poisoning and Procedural Complications			Contusion, medication error	
^a Adverse reactions in the Investigations system organ class (SOC) have been reallocated to clinically appropriate SOCs related to their target organ. Different MedDRA preferred terms that were considered clinically similar have been grouped into a single term.				

Other clinical studies with Teysuno in combination with cisplatin

Although studies of Teysuno in combination with cisplatin that were conducted in Japan utilised doses and dosing schedules that differed from this regimen, the safety profile from these studies was similar, with the most common toxicities being haematologic, gastrointestinal, fatigue, and anorexia.

Paediatric population

No studies have been performed with Teysuno alone or in combination with cisplatin in paediatric patients.

Post-marketing surveillance experience in gastric cancer patients

The safety profile of Teysuno in a post-marketing safety surveillance study in Japan of 4,177 patients treated with Teysuno for advanced gastric cancer was generally similar to that seen with this regimen and in the Japanese registration studies (i.e., major toxicities were leukocytopenia, anorexia, and nausea/vomiting).

Description of selected adverse reactions

Ocular toxicity

Terms for treatment-related ocular toxicities have been combined as follows. The only Grade 3 or higher adverse reaction was reduced visual acuity.

- Vision disorder includes adverse reactions of blurred vision, diplopia, photopsia, reduced visual acuity, and blindness;
- Lacrimal disorder includes adverse reactions of increased lacrimation, dry eye, and acquired dacryostenosis;
- Eye disorder includes adverse reactions of eye pruritus, ocular hyperaemia, eye irritation, eye disorder, and foreign body sensation in eyes.

Neuropathy

Central and peripheral neuropathy has been reported in patients treated with Teysuno in combination with cisplatin. The term peripheral neuropathy includes the following reported adverse reactions: peripheral sensory neuropathy, paraesthesia, hypoaesthesia, peripheral neuropathy, polyneuropathy, neurotoxicity, and dysaesthesia.

Special populations

Elderly (see section 4.2)

Comparison of safety between 71 patients ≥ 70 years old (elderly) and 450 patients < 70 years old treated with Teysuno in combination with cisplatin in the FLAGS study demonstrated that the incidence of all Grade 3 or higher adverse reactions (62% vs 52%), all serious adverse reactions (30% vs 19%), and the rate of premature withdrawal due to adverse reactions from both Teysuno and cisplatin (21% vs 12%) appeared to be higher among patients ≥ 70 years old. A population pharmacokinetics analysis demonstrated that 5-FU exposure also tended to increase with age, but the

extent of the increase was within the range of individual variability. These changes with age were related to changes in renal function as measured by creatinine clearance (see section 5.2).

Gender

There were no clinically relevant differences in safety between males (N=382) and females (N=139) in the FLAGS study.

Patients with renal impairment (see sections 4.2, 4.3, 4.4, and 5.2)

Comparison of 218 patients with mild renal impairment at baseline (CrCl 51 to 80 ml/min) to 297 patients with normal renal function at baseline (CrCl >80 ml/min) treated with Teysuno in combination with cisplatin in the FLAGS study indicated that there were no clinically significant differences in safety between patients with mild renal impairment and patients with normal renal function.

In a study performed in patients with renal impairment, 7 patients with moderate renal impairment were treated with 20 mg/m² Teysuno. No dose limiting toxicities were observed and no dose reductions were needed among these patients. The most common adverse reactions were diarrhoea, nausea, and vomiting; no Grade 3 or higher adverse reactions were reported.

4.9 Overdose

The highest single dose of Teysuno taken was 1400 mg; this patient developed leukopenia (Grade 3). Manifestations of acute overdose reported include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation, bleeding, bone marrow depression, and respiratory failure. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

There is no known antidote available in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites, ATC code: L01BC53.

Mechanism of action

Teysono is an oral fluoropyrimidine anti-cancer medicinal product. It is a fixed dose combination of three active substances, tegafur, which after absorption is converted into the anti-cancer substance 5-FU; gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor to prevent degradation of 5-FU by the body; and, oteracil, an orotate phosphoribosyltransferase (OPRT) inhibitor that decreases the activity of 5-FU in normal gastrointestinal mucosa. The combination of tegafur, gimeracil, and oteracil was set at 1:0.4:1 molar ratio as optimum in order to maintain 5-FU exposure and thus sustain anti-tumour activity while reducing toxicity associated with 5-FU alone.

Tegafur is a prodrug of 5-FU with good oral bioavailability. Following oral administration, tegafur is gradually converted to 5-FU *in vivo*, mainly by CYP2A6 enzyme activity in the liver. 5-FU is metabolised by the liver enzyme DPD. 5-FU is activated within cells by phosphorylation to its active metabolite, 5-fluoro-deoxyuridine-monophosphate (FdUMP). FdUMP and reduced folate are bound to thymidylate synthase leading to formation of a ternary complex which inhibits DNA synthesis. In addition, 5-fluorouridine-triphosphate (FUTP) is incorporated into RNA causing disruption of RNA functions.

Gimeracil inhibits the metabolism of 5-FU by reversibly and selectively inhibiting DPD, the primary metabolic enzyme for 5-FU, so that higher plasma concentrations of 5-FU are achieved with the administration of a lower dose of tegafur.

After oral administration, oteracil was distributed at high concentrations in normal gastrointestinal tract tissues while considerably lower concentrations were seen in blood and tumour tissue in animal studies.

Pharmacodynamic effects

In a dose escalation study comparing the tolerability of 5-FU in Teysuno and tegafur + gimeracil (no oteracil), the 25 mg/m² dose level could not be attained in the absence of oteracil due to the occurrence of dose limiting toxicities (Grade 3 diarrhoea in 2 patients, and cardio-respiratory arrest in 1 patient) in the tegafur+gimeracil arm. The 5-FU pharmacokinetic profile was similar in the presence and absence of oteracil.

Mean 5-FU maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values were approximately 3-fold higher after Teysuno administration than after administration of tegafur alone, despite a 16-fold lower Teysuno dose (50 mg of tegafur) compared to tegafur alone (800 mg), and are attributed to inhibition of DPD by gimeracil. Maximum plasma uracil concentration was observed at 4 hours, with a return to baseline levels within approximately 48 hours after dosing, indicating the reversibility of the DPD inhibition by gimeracil.

A study of the effect of Teysuno on cardiac repolarisation conducted in advanced cancer patients met the definition for a negative study according to International Conference on Harmonisation (ICH) guidelines. No consistent relationship was seen between absolute QTcF interval values or change from Baseline values and maximum plasma concentration of Teysuno components.

A Phase I study established the current regimen by evaluating cohorts of Teysuno and cisplatin of 30 mg/m² and 60 mg/m² (dose-limiting toxicities [DLTs] seen were fatigue, and diarrhoea and dehydration); 25 mg/m² and 60 mg/m²; and 25 mg/m² and 75 mg/m². Despite the lack of DLTs in the last cohort, the dose of cisplatin was not elevated beyond 75 mg/m².

In the Phase III FLAGS study, there was no apparent relationship between 5-FU AUC (Teyuno/cisplatin arm) and 5-FU concentration (5-FU/cisplatin arm) during Cycle 1 and efficacy outcomes of overall survival (OS) or progression-free survival (PFS).

Advanced gastric cancer:

Data from a multicentre, multinational (excluding Asia), randomised, controlled, open-label Phase III clinical study (FLAGS) support the use of Teysuno in combination with cisplatin for the treatment of patients with advanced gastric cancer. In this study, 521 patients were randomised to treatment with Teysuno (25 mg/m² orally twice daily for 21 days followed by a 7-day rest period) and cisplatin (75 mg/m² intravenous infusion once every 4 weeks); and 508 patients were randomised to treatment with 5-FU (1000 mg/m²/24 hours as a continuous intravenous infusion on Days 1 through 5 repeated every 4 weeks) and cisplatin (100 mg/m² as an intravenous infusion on Day 1 repeated every 4 weeks). Patient characteristics are provided in Table 8.

Table 8: Demographics and baseline characteristics of patients in the FLAGS study

	Teysuno + Cisplatin 75 mg/m² (N=521)	5-FU + Cisplatin 100 mg/m² (N=508)
Gender, n (%)		
Male	382 (73)	347 (68)
Female	139 (27)	161 (32)
Age, years		
Median (Range)	59 (18-83)	60 (20-85)
≥65, n (%)	160 (31)	164 (32)
Race, n (%)		
White	447 (86)	438 (86)
Black or African American	5 (1.0)	7 (1.4)
Asian	4 (0.8)	4 (0.8)
American Indian or Alaska Native	4 (0.8)	6 (1.2)
Other	61 (12)	53 (10)
ECOG Performance Status, n (%)		
0	226 (43)	200 (39)
1	295 (57)	308 (61)
Location of primary lesion, n (%)		
Stomach	438 (84)	417 (82)
Gastro-oesophageal junction	82 (16)	88 (17)
Both	1 (0.2)	3 (0.6)
Metastatic disease, n (%)		
≥2 metastatic sites	497 (95)	488 (96)
	340 (65)	327 (64)

For the primary endpoint of overall survival, Teysuno in combination with cisplatin was non-inferior to 5-FU in combination with cisplatin (see Table 9). At the time of primary analysis, the median follow-up for overall survival in the full analysis set was 18.3 months.

Table 9: Overall survival and progression-free survival in FLAGS

Endpoint	Teysuno + Cisplatin		5-FU + Cisplatin		Hazard Ratio [95% CI]
	N	Median [95% CI], months	N	Median [95% CI], months	
Overall Survival					
Intent-to-treat	527	8.5 [7.9, 9.3]	526	7.9 [7.2, 8.5]	0.94 [0.82, 1.07]
Full analysis set	521	8.6 [7.9, 9.5]	508	7.9 [7.2, 8.5]	0.92 [0.80, 1.05]
Progression-free Survival					
Full analysis set	521	4.8 [4.0, 5.5]	508	5.5 [4.4, 5.8]	0.99 [0.86, 1.14]

CI = confidence interval; Full analysis set = all randomised, treated patients analysed as allocated (primary analysis population)

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Teysuno in all subsets of the paediatric population in gastric adenocarcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The single and multiple dose pharmacokinetics (PK) of Teysuno in combination with cisplatin were evaluated in three studies. Eighteen additional PK studies were performed using the relevant regimen as monotherapy. All studies were performed in cancer patients.

Absorption

After administration of a single dose of 50 mg Teysuno (expressed as tegafur content) in man (approximately 30 mg/m² based on body surface area of 1.56 to 2.10 m² for a typical patient; N=14), the median T_{max} for Teysuno components tegafur, gimeracil, and oteracil was 0.5, 1.0, and 2.0 hours, respectively, and the mean ± standard deviation (SD) AUC_{0-inf} and C_{max} was 14595 ± 4340 ng.hr/ml and 1762 ± 279 ng/ml for tegafur, 1884 ± 640 ng.hr/ml and 452 ± 102 ng/ml for gimeracil, 556 ± 281 ng.hr/ml and 112 ± 52 ng/ml for oteracil. The median T_{max} for 5-FU was 2.0 hours and the mean AUC_{0-inf} and C_{max} was 842 ± 252 ng.hr/ml and 174 ± 58 ng/ml. Levels of tegafur, gimeracil, oteracil and 5-FU were quantifiable through 10 hours postdose. After administration of 30 mg/m² doses, steady-state conditions are reached for tegafur, gimeracil, and oteracil at the latest by Day 8.

After multiple dose administration (30 mg/m², expressed as tegafur content, twice daily for 14 days; N=10), the median T_{max} of tegafur, gimeracil, and oteracil was 0.8, 1.0, and 2.0 hours, respectively, and the corresponding mean ± SD AUC_(0-12h) and C_{max} was 19967 ± 6027 ng.hr/ml and 2970 ± 852 ng/ml for tegafur, 1483 ± 527 ng.hr/ml and 305 ± 116 ng/ml for gimeracil, and 692 ± 529 ng.hr/ml and 122 ± 82 ng/ml for oteracil. The median T_{max} for 5-FU was 2.0 hours and the mean AUC_(0-12h) and C_{max} was 870 ± 405 ng.hr/ml and 165 ± 62 ng/ml, respectively.

Administration of Teysuno under fed conditions resulted in decreased AUC_{0-inf} for oteracil of approximately 71% and gimeracil of approximately 25% relative to fasting administration. Concomitant administration of a proton pump inhibitor (PPI) reduced the effect of food on the pharmacokinetic profile of oteracil, but not by a sufficient margin to completely negate the food effect. There was a 15% decrease in AUC_{0-inf} for 5-FU under fed versus fasting conditions, and tegafur exposure was not altered by food (thus demonstrating absence of a food effect).

Mean AUC_{0-inf} and C_{max} for 5-FU were approximately 3-fold greater following administration of Teysuno (50 mg expressed as tegafur content) than following administration of tegafur alone (800 mg), while AUC_{0-inf} and C_{max} values for the 5-FU metabolite α-fluoro-β-alanine (FBAL) were approximately 15- to 22-fold lower following administration of Teysuno than following administration of tegafur.

The oteracil component of Teysuno did not affect the pharmacokinetic profiles of 5-FU, tegafur, gimeracil, FBAL, or uracil. The gimeracil component did not affect the pharmacokinetic profile of tegafur.

Distribution

Oteracil, gimeracil, 5-FU, and tegafur were 8.4%, 32.2%, 18.4%, and 52.3% protein bound, respectively. The protein binding in human serum was not concentration-dependent over a range of 0.1 to 1.0 µg/ml for oteracil, gimeracil, and 5-FU and 1.2 to 11.8 µg/ml for tegafur.

There are no clinical data on the distribution of radiolabeled components of Teysuno. Although no intravenous data are available for Teysuno in humans, the volume of distribution could be roughly estimated from the apparent volume of distribution and urinary excretion data as 16 l/m², 17 l/m², and 23 l/m² for tegafur, gimeracil and oteracil, respectively.

Biotransformation

The main metabolic pathway for tegafur is through conversion to 5-FU via CYP2A6 in the liver, whereas gimeracil was stable in human liver homogenate (S9 fraction) with adenosine 3'-phosphate 5'-phosphosulphate lithium salt (PAPS; a co-factor for sulfotransferase) or nicotinamide adenine dinucleotide phosphate (NADPH). Based on the results of *in vitro* studies, a part of oteracil is non-enzymatically degraded to 5-azauracil (5-AZU) by gastric fluid, and is then converted to cyanuric acid (CA) in the digestive tract. 5-AZU and CA do not inhibit OPRT enzyme activity. Only a small amount of oteracil is metabolised in the liver because of its low permeability.

In vitro evaluation using human liver microsomes indicated that neither tegafur, gimeracil nor oteracil showed any relevant inhibitory effects on enzyme activities of the cytochrome P450 isoforms tested (i.e., CYP1A1/2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4).

In vitro evaluation using primary cultures of human hepatocytes indicated that tegafur (0.7-70 μM), gimeracil (0.2-25 μM) and oteracil (0.04-4 μM) had little or no inductive effect on CYP1A2, CYP2B6 or CYP3A4/5 metabolic activities.

Using plasma uracil concentrations to assess DPD activity in clinical studies, no marked changes in plasma uracil concentrations were observed after administration of a single 800 mg dose of tegafur while plasma uracil concentrations increased markedly after administration of a single 50 mg dose of Teysuno (reflecting DPD inhibition by gimeracil). Following both single dose (50 mg) and multiple dose (30 mg/m² twice daily) administration of Teysuno in man, maximum uracil concentrations reflecting DPD inhibition were observed approximately 4 hours postdose. Similar inhibition was seen following single and multiple dosing. The plasma concentrations of uracil returned to baseline levels approximately 48 hours after dosing indicating reversibility of DPD inhibition by gimeracil.

Elimination

In man, the apparent terminal elimination half-life ($T_{1/2}$) of 5-FU observed after administration of Teysuno (containing tegafur, a 5-FU prodrug) was longer (approximately 1.6 - 1.9 hours) than that previously reported after intravenous administration of 5-FU (10 to 20 minutes). Following a single dose of Teysuno, $T_{1/2}$ values ranged from 6.7 to 11.3 hours for tegafur, from 3.1 to 4.1 hours for gimeracil, and from 1.8 to 9.5 hours for oteracil.

Following a single dose of Teysuno, approximately 3.8% to 4.2% of administered tegafur, 65% to 72% of administered gimeracil, and 3.5% to 3.9% of administered oteracil were excreted unchanged in the urine. Among the metabolites, 9.5% to 9.7% of the administered tegafur was excreted in the urine as 5-FU and approximately 70% to 77% as FBAL, accounting for approximately 83% to 91% of the administered Teysuno dose (total tegafur + 5-FU + FBAL). There was no effect of gimeracil on renal clearance of tegafur, FBAL, and 5-FU following administration of Teysuno as compared to their clearance following administration of tegafur alone.

Linearity/non-linearity

In a Japanese Phase I study that utilized 5 dose groups with doses ranging from 25 to 200 mg/body, there was a dose-proportional increase in exposure for tegafur, gimeracil and oteracil. However, the increase in 5-FU exposure tended to be greater than proportional to the increasing tegafur dose.

Pharmacokinetics in special populations

Population PK

A population PK analysis of Teysuno components and metabolites assessed the influence of various factors, including gender, age, food, ethnicity (Caucasian vs Asian), renal function, and hepatic function in 315 patients. Renal function, as reflected by creatinine clearance, was the primary factor that influenced gimeracil exposure and 5-FU exposure. As renal function decreased, there was an increase in 5-FU steady state exposure. This analysis also demonstrated that the trend in changes in Teysuno pharmacokinetics observed with increasing age was related to change in renal function as measured by creatinine clearance.

Renal impairment

In a Phase I Teysuno monotherapy study that investigated the pharmacokinetics of components and metabolites in patients with normal and impaired renal function, patients with mild renal impairment (CrCl 51 to 80 ml/min) receiving the same monotherapy dose of 30 mg/m² twice daily (the maximum tolerated dose for monotherapy) as patients with normal renal function (CrCl >80 ml/min) had an

increase in mean 5-FU AUC_{0-inf} relative to that of the normal patients. Patients with moderate renal impairment (CrCl 30 to 50 ml/min) who received a reduced dose of 20 mg/m² twice daily showed no significant increase in mean 5-FU AUC_{0-inf} relative to that of the normal group. The increase in 5-FU exposure in patients with mild renal impairment in this study together with the results of simulation in the population pharmacokinetic analysis suggest that a Teysuno dose of 25 mg/m² twice daily in patients with mild renal impairment could achieve 5-FU plasma concentrations similar to those obtained in patients with normal renal function receiving 30 mg/m² twice daily as monotherapy and also those with moderate renal impairment receiving 20 mg/m² twice daily.

Hepatic impairment

There were no significant differences in AUCs of 5-FU, tegafur, gimeracil, or oteracil after either single or multiple dose administration of Teysuno 30 mg/m² twice daily in patients with mild, moderate, or severe hepatic impairment compared to those with normal hepatic function. After single dose administration, there was a statistically significant decrease in 5-FU and gimeracil C_{max} for the severe hepatic impairment group relative to that of the normal group, but this difference was not observed after multiple dose administration.

Ethnic differences

A Phase I study investigated the pharmacokinetics of Teysuno monotherapy in Asian (Chinese/Malay) and Caucasian (US) patients. Consistent with the lower CYP2A6 activity in the Asian patients, tegafur AUC₀₋₁₂ was higher and T_{1/2} was longer in the Asian group compared to the Caucasian group. Gimeracil and uracil AUC₀₋₁₂ values were comparable between the two groups, suggesting that DPD inhibition was similar for the Asian and Caucasian groups. Exposure of 5-FU was not statistically significantly different between the two groups. Oteracil AUC₀₋₁₂ in the Asian group was approximately half that of the Caucasian group, however, this difference was not statistically significant due to its large individual variability.

Studies in Japanese patients have suggested an effect of CYP2A6*4 polymorphism on Teysuno pharmacokinetics. Although CYP2A6 variants are associated with pharmacokinetic variability of tegafur, the AUC of gimeracil, which is affected by renal function, is the key determinant in the pharmacokinetic variability of 5-FU. In the Phase III (FLAGS) study, tegafur AUC was significantly higher in patients with the CYP2A6*4 allele, however, no significant difference was found for 5-FU AUC and for the incidence of adverse reactions. Therefore, the CYP2A6 polymorphism differences between Asian and Western populations do not appear to be the key determinant for differences in the MTD between populations. However, limited data available on CYP2A6*4/*4 genotype in Japanese patients treated with Teysuno suggest significantly decreased 5-FU levels in this subpopulation. No dose advice for this subpopulation can be provided. This CYP2A6*4 allele is uncommon in the Caucasian population.

Paediatric population

No pharmacokinetic studies have been conducted with Teysuno in paediatric patients.

5.3 Preclinical safety data

Repeat-dose toxicity studies in rats, dogs and monkeys produced changes typically associated with administration of an anti-cancer medicinal product eliciting cytotoxic effects on populations of rapidly dividing cells, such as anaemia, decrease in the immune and digestive system function, disruption of spermatogenesis, and atrophy in male and female reproductive organs.

Treatment with Teysuno produced various skin effects in rat (keratosis of footpad and tail) and dog (skin crusts and erosions). In addition, hyperpigmentation in the skin and eyes and corneal opacity in dogs and cataracts in rats were observed following repeat dosing. These changes were reversible.

Teysuno does not appear to affect male or female fertility in the rat; however, administration at any time after conception resulted in a range of external, visceral, and skeletal foetal abnormalities in rat and rabbit. There is therefore a high risk for developmental toxicity at clinical doses, primarily due to tegafur (5-FU) and to oteracil to a lesser extent.

Teysuno was not carcinogenic in either the rat or the mouse. Teysuno was not found to be mutagenic when tested in the *in vitro* Ames assay. Teysuno was clastogenic *in vitro* using Chinese hamster lung cells and was weakly clastogenic *in vivo* in mouse bone marrow.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Lactose monohydrate

Magnesium stearate

Capsule shell

Gelatin

Red iron oxide (E172)

Titanium dioxide (E171)

Sodium lauryl sulphate

Talc

Ink

Red iron oxide (E172)

Yellow iron oxide (E172)

FD&C Blue No. 2 aluminium lake (E132)

Carnauba wax

Bleached shellac

Glyceryl monooleate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PCTFE/PVC/Al opaque blisters containing either 42 capsules (3 blisters containing 14 capsules each) or 126 capsules (9 blisters containing 14 capsules each).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Hands should be washed after handling capsules.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Taiho Pharma Europe, Limited
55 Colmore Row, Birmingham
West Midlands, B3 2AS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Teysuno 20 mg/5.8 mg/15.8 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg tegafur, 5.8 mg gimeracil and 15.8 mg oteracil (as 19.6 mg of oteracil monopotassium).

Excipient(s)

Each hard capsule contains 93.6 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

The capsule has an opaque white body and opaque white cap imprinted "TC442" in grey.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin (see section 5.1).

4.2 Posology and method of administration

Teysuno should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products.

Posology

The recommended standard dose of Teysuno when administered in combination with cisplatin is 25 mg/m² (expressed as tegafur content) twice daily, morning and evening, for 21 consecutive days followed by 7 days rest (1 treatment cycle). This treatment cycle is repeated every 4 weeks.

The standard and reduced Teysuno and cisplatin doses and calculations according to body surface area (BSA) for doses of Teysuno given in combination with cisplatin are provided in Table 1 and Table 2, respectively. The patient's BSA must be recalculated and the Teysuno dose adjusted accordingly if a patient's weight increases or decreases by $\geq 10\%$ from the one used for the previous calculation of BSA and the change is clearly not related to fluid retention.

The recommended dose of cisplatin with this regimen is 75 mg/m² by intravenous infusion administered once every 4 weeks. Cisplatin should be discontinued after 6 cycles without withdrawal of Teysuno. If cisplatin is discontinued before 6 cycles, Teysuno treatment alone can be resumed when the criteria for restarting it are met.

Patients treated with Teysuno in combination with cisplatin should be closely monitored and laboratory tests, including haematology, liver function, renal function, and serum electrolytes, should be performed frequently. Treatment should be discontinued if progressive disease or intolerable toxicity is observed.

Refer to the cisplatin summary of product characteristics (SmPC) for pretreatment hyperhydration.

Patients should be provided with outpatient prescriptions for anti-emetic and anti-diarrhoeal medicinal products.

Teysuno doses

Table 1: Standard dose and dose reductions allowed for Teysuno and/or for cisplatin

Medicinal product	Standard dose (mg/m ²)		Dose reduction 1 (mg/m ²)		Dose reduction 2 (mg/m ²)
Teysuno	25 ^a	→	20 ^a	→	15 ^a
and/or					
Cisplatin	75	→	60	→	45

^a Expressed as tegafur content.

Teysuno dose calculations

Table 2: Standard and reduced dose calculations by body surface area (m²)

Teysuno dose	Each dose in mg (each dosing) ^a	Total daily dose in mg ^a	Number of capsules for each dose (2 doses/day)	
			15 mg capsule ^a (brown/white)	20 mg capsule ^a (white)
Standard dose^a: 25 mg/m²				
BSA ≥ 2.30 m ²	60	120	0	3
BSA = 2.10 - 2.29 m ²	55	110	1	2
BSA = 1.90 - 2.09 m ²	50	100	2	1
BSA = 1.70 - 1.89 m ²	45	90	3	0
BSA = 1.50 - 1.69 m ²	40	80	0	2
BSA = 1.30 - 1.49 m ²	35	70	1	1
BSA ≤ 1.29 m ²	30	60	2	0
First dose reduction^a: to 20 mg/m²				
BSA ≥ 2.13 m ²	45	90	3	0
BSA = 1.88 - 2.12 m ²	40	80	0	2
BSA = 1.63 - 1.87 m ²	35	70	1	1
BSA = 1.30 - 1.62 m ²	30	60	2	0
BSA ≤ 1.29 m ²	20	40	0	1
Second dose reduction^a: to 15 mg/m²				
BSA ≥ 2.17 m ²	35	70	1	1
BSA = 1.67 - 2.16 m ²	30	60	2	0
BSA = 1.30 - 1.66 m ²	20	40	0	1
BSA ≤ 1.29 m ²	15	30	1	0

Calculate BSA to 2 decimal places.
^a Expressed as tegafur content.

Adjustments during treatment

General

Toxicity due to Teysuno administration should be managed with symptomatic treatment and/or treatment interruption or dose reduction. Patients taking Teysuno should be informed of the risks and instructed to contact their physician immediately if moderate or severe toxicity occurs.

Doses omitted for toxicity are not replaced; and, if a patient vomits after taking a dose, this dose should not be replaced.

Once the Teysuno dose has been reduced, it should not be increased again.

Teysuno dose modification criteria

Dose modifications for toxicity should be made according to Tables 1, 3, 4, and 5. A maximum of two consecutive dose reductions for each medicinal product, as described in Table 1, can be applied in case of toxicity. Each dose reduction results in approximately 20-25% reduction of dose. See Table 2 for the details of the number of Teysuno capsules to be administered for each dose level. For minimum criteria for resumption of Teysuno treatment, see Table 6.

Teysuno dose modifications for toxicity when used in combination with cisplatin can be made in two ways.

- *During a 4-week cycle of treatment*

Teysuno should only be given on Days 1 to 21 of each cycle, i.e., treatment should not be given on Days 22 to 28 of a cycle. Treatment days missed in a cycle where drug was held due to toxicity should not be replaced.

During a treatment cycle, dose adjustment should be performed for each individual medicinal product that is considered to be causally related to the toxicity, if such a distinction can be made. If both medicinal products are considered to be causing the toxicity or it is not possible to distinguish them, then dose reduction should be performed for both according to the recommended dose reduction schedule.

- *At the initiation of subsequent cycles of treatment*

If a treatment delay is indicated for either Teysuno or cisplatin, then administration of both medicinal products should be delayed until the requirements for restarting both are met unless one of the medicinal products has been permanently discontinued.

Dose modifications for Teysuno for adverse reactions in general except for haematologic and renal toxicities

Table 3: Teysuno dose reduction schedule for treatment-related toxicities in general, except for haematologic and renal toxicities

Toxicity grades ^a	Teysono dose changes within a 21-day treatment cycle	Teysono dose adjustment for next dose / next cycle
Grade 1		
Any occurrence	Maintain treatment at same dose level	None
Grade 2^{b,c}		
Any occurrence	Suspend treatment until Grade 0 or 1	None
Grade 3 or Higher^c		
First occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from previous level
Second occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from previous level
Third occurrence	Discontinue treatment	Discontinue treatment
^a According to the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. ^b For Grade 2 nausea and/or vomiting, the anti-emetic therapy should be optimized prior to a suspension of Teysuno. ^c At the discretion of the treating physician, patients may continue with treatment without reduction or interruption for adverse reactions (irrespective of grade) considered unlikely to become serious or life-threatening (e.g., alopecia, changes in sexual function, and dry skin).		

Dose modifications for renal toxicities

Creatinine clearance (CrCl) must be determined for every cycle before the start of treatment on Day 1.

Table 4: Teysuno and cisplatin dose modification according to creatinine clearance values at the start of a cycle of treatment

Creatinine clearance	Teysono dose modification at the start of the cycle of treatment	Cisplatin dose modification at the start of the cycle of treatment
≥50 ml/min	No dose modification	No dose modification
30 to 49 ml/min	Start treatment at one reduced dose level	Start cisplatin treatment at a 50% dose reduction from the previous cycle
≤30 ml/min	Suspend treatment until resumption criterion (≥30 ml/min) is met and then start treatment at one reduced dose level	Suspend cisplatin treatment until resumption criterion (≥30 ml/min) is met and then start treatment at a 50% dose reduction from the previous cycle

Dose modifications for haematologic toxicities

Table 5: Haematologic toxicities for which Teysuno treatment should be suspended

Units	Neutrophils	Platelets	Haemoglobin	Teysono dose modification
IU	<0.5 x 10 ⁹ /l	<25 x 10 ⁹ /l	4.0 mmol/l	Suspend treatment until resumption criterion is met (see Table 6) and then resume dosing at one reduced dose level.

Resumption criteria for Teysuno treatment

Table 6: Minimum criteria to resume Teysuno treatment following its suspension due to a toxicity

Non-haematologic	Haematologic
Baseline or Grade 1	Platelet count $\geq 100 \times 10^9/l$
Calculated creatinine clearance ≥ 30 ml/min	Neutrophils $\geq 1.5 \times 10^9/l$
	Haemoglobin ≥ 6.2 mmol/l
CrCl must be calculated at the beginning of every cycle before the start of treatment with Teysuno on Day 1.	

Dose modifications for special populations

Renal impairment

- Mild renal impairment (CrCl 51 to 80 ml/min)

No adjustment of the standard dose is recommended in patients with mild renal impairment (see section 5.2).

- Moderate renal impairment (CrCl 30 to 50 ml/min)

The recommended standard dose in patients with moderate renal impairment is 20 mg/m² twice daily (expressed as tegafur content) (see sections 4.8 and 5.2).

- Severe renal impairment (CrCl below 30 ml/min)

Use is contraindicated in severe renal impairment (see sections 4.3 and 4.4).

Elderly

No adjustment of the standard dose is recommended in patients ≥ 70 years old (see section 4.8).

Hepatic impairment

No adjustment of the standard dose is recommended for patients with hepatic impairment (see section 5.2).

Ethnicity

No adjustment of the standard dose is recommended for patients of Asian ethnicity (see section 5.2).

Paediatric population

The safety and efficacy of Teysuno in children and adolescents under 18 years old have not been established. No data are available. Therefore, Teysuno should not be administered to children or adolescents under 18 years of age.

Method of administration

Capsules should be taken by mouth with water at least 1 hour before or 1 hour after a meal (see section 5.2).

4.3 Contraindications

- Hypersensitivity to any of the active substances (tegafur, gimeracil, and oteracil) or to any of the excipients (see sections 4.4 and 6.1).
- History of severe and unexpected reactions to fluoropyrimidine therapy.
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Pregnancy and breastfeeding.
- Severe bone marrow suppression (severe leukopaenia, neutropaenia, or thrombocytopaenia; see section 4.2, Table 5).
- Severe renal impairment (CrCl below 30 ml/min).
- Co-administration of other fluoropyrimidines with Teysuno.
- Treatment within 4 weeks with DPD inhibitors, including sorivudine or its chemically related analogues such as brivudine.
- Contraindications for cisplatin; refer to the cisplatin SmPC.

4.4 Special warnings and precautions for use

Dose limiting toxicities include diarrhoea and dehydration. Most adverse reactions are reversible and can be managed by symptomatic therapy, dose interruptions and dose reductions.

Bone marrow suppression

Treatment-related bone marrow suppression, including neutropaenia, leukopaenia, thrombocytopaenia, anaemia, and pancytopaenia, has been reported among patients treated with Teysuno in combination with cisplatin. Patients with low white blood cell counts should be monitored carefully for infection and risk of other complications of neutropaenia and treated as medically indicated (e.g., with antibiotics, granulocyte-colony stimulating factor [G-CSF]). Patients with low platelet counts are at increased risk for bleeding and should be monitored carefully. The dose should be modified as recommended in section 4.2.

Diarrhoea

Patients with diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Prophylactic treatment for diarrhoea should be administered as indicated. Standard anti-diarrhoeal therapy (e.g., loperamide) and intravenous fluids/electrolytes should be initiated early when diarrhoea develops. Dose suspension/adjustment should be implemented with the occurrence of Grade 2 or higher diarrhoea if symptoms persist despite adequate treatment.

Dehydration

Dehydration and any associated electrolyte disturbances should be prevented or corrected at onset. Patients with anorexia, asthenia, nausea, vomiting, diarrhoea, stomatitis, and gastrointestinal obstruction should be monitored closely for signs of dehydration. Dehydration should be managed aggressively with rehydration and other appropriate measures. If Grade 2 (or higher) dehydration occurs, treatment should be immediately suspended and the dehydration corrected. Treatment should not be resumed until dehydration and its underlying causes are corrected or adequately controlled. Dose modifications should be applied for the precipitating adverse reaction as necessary (see section 4.2).

Renal toxicity

Treatment with Teysuno in combination with cisplatin may be associated with a transient decline of glomerular filtration rate caused primarily by pre-renal factors (e.g., dehydration, electrolyte imbalance, etc). Adverse reactions of Grade 3 or higher such as increased blood creatinine, decreased creatinine clearance, toxic nephropathy, and acute renal failure have all been reported in patients receiving Teysuno in combination with cisplatin (see section 4.8). To detect early changes in renal function during treatment, renal parameters should be closely monitored (e.g., serum creatinine, CrCl). If deterioration of glomerular filtration rate is observed, Teysuno and/or cisplatin dose should be adjusted according to Table 4, and appropriate supportive measures taken (see section 4.2).

Dehydration and diarrhoea may increase the risk of renal toxicity for cisplatin. Hyperhydration (forced diuresis) should be administered according to the cisplatin SmPC to reduce the risk of renal toxicity associated with cisplatin therapy.

Gimeracil increases 5-fluorouracil (5-FU) exposure by inhibiting DPD, the primary enzyme for metabolizing 5-FU. Gimeracil is primarily cleared by the kidney (see section 5.2); so, in patients with renal insufficiency gimeracil renal clearance is decreased and 5-FU exposure thus increased. Treatment-related toxicities can be expected to increase as 5-FU exposure increases (see section 5.2).

Ocular toxicity

The most common treatment-related ocular disorders among patients in studies in Europe/United States of America (EU/USA) treated with Teysuno in combination with cisplatin were lacrimal disorders (8.8%), including increased lacrimation, dry eye, and acquired dacryostenosis (see section 4.8).

Most ocular reactions will resolve or improve with suspension of medicinal product and proper treatment (instillation of artificial tears, antibiotic eye drops, implantation of glass or silicone tubes in lacrimal punctas or canaliculi, and/or use of spectacles rather than contact lenses). Efforts should be made to ensure early detection of ocular reactions, including an early ophthalmologic consultation in the event of any persistent or vision-reducing ocular symptoms such as lacrimation or corneal symptoms.

Refer to the cisplatin SmPC for eye disorders observed with cisplatin therapy.

Coumarin-derivative anticoagulant

Patients receiving oral coumarin-derivative anticoagulant therapy must have their anticoagulant response (International Normalized Ratio for prothrombin time [INR] or prothrombin time [PT]) monitored closely and the anticoagulant dose adjusted accordingly (see section 4.5). The use of coumarin-derivative anticoagulant in clinical trials has been associated with elevated INR and gastrointestinal bleeding, bleeding tendency, haematuria, and anaemia in patients receiving Teysuno therapy.

DPD inducers

If a DPD inducer were to be concomitantly administered with Teysuno, the exposure of 5-FU might not reach the efficacious level. However, since no DPD inducers are currently known, the interaction between a DPD inducer and Teysuno can not be evaluated.

Microsatellite instability (MSI)

Teysuno has not been studied in gastric cancer patients with MSI. The association between 5-FU sensitivity and MSI in patients with gastric cancer is unclear and the association between Teysuno and MSI in gastric cancer is unknown.

Glucose/galactose intolerance/malabsorption

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose/galactose malabsorption should not take this medicinal product.

Other oral fluoropyrimidines

No clinical trials are available comparing Teysuno versus other oral 5-FU compounds. Therefore, Teysuno cannot be used as a substitute for other oral 5-FU products.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products

No interaction studies have been performed in adult or paediatric patients.

Other fluoropyrimidines

Co-administration of other fluoropyrimidines such as capecitabine, 5-FU, tegafur, or flucytosine can lead to additive toxicities, and is contraindicated. A minimum washout period of 7 days is recommended between administration of Teysuno and other fluoropyrimidines. The washout period described in the SmPC of other fluoropyrimidine medicinal products should be followed if Teysuno is to be administered subsequent to other fluoropyrimidine medicinal products.

Sorivudine and brivudine

Sorivudine or its chemically related analogues such as brivudine irreversibly inhibit DPD, resulting in a significant increase in 5-FU exposure. This may lead to increased clinically significant fluoropyrimidine-related toxicities with potentially fatal outcomes. Teysuno must not be used with sorivudine or brivudine or within 4 weeks of the last dose of sorivudine or brivudine.

CYP2A6 inhibitors

As CYP2A6 is the major enzyme responsible for the conversion of tegafur to 5-FU, co-administration of a known CYP2A6 inhibitor and Teysuno should be avoided as effectiveness of Teysuno could be decreased (see section 5.2).

Folate/folinic acid

No data are available on the concomitant use of folinic acid with Teysuno in combination with cisplatin. However, metabolites of folinate/folinic acid will form a ternary structure with thymidylate

synthase and fluorodeoxyuridine monophosphate (FdUMP), potentially increasing the cytotoxicity of 5-FU. Caution is advised as folinic acid is known to enhance the activity of 5-FU.

Nitroimidazoles, including metronidazole and misonidazole

No data are available on the concomitant use of nitroimidazoles with Teysuno in combination with cisplatin. However, nitroimidazoles may reduce clearance of 5-FU and thus increase plasma levels of 5-FU. Caution is advised as co-administration may increase the toxicity of Teysuno.

Methotrexate

No data are available on the concomitant use of methotrexate with Teysuno in combination with cisplatin. However, polyglutamated methotrexate inhibits thymidylate synthase and dihydrofolate reductase, potentially increasing cytotoxicity of 5-FU. Caution is advised as co-administration may increase the toxicity of Teysuno.

Clozapine

No data are available on the concomitant use of clozapine with Teysuno in combination with cisplatin. However, due to possible additive pharmacodynamic effects (myelotoxicity), caution is advised as co-administration may increase the risk and severity of haematologic toxicity of Teysuno.

Cimetidine

No data are available on the concomitant use of cimetidine with Teysuno in combination with cisplatin. However, co-administration may decrease clearance and, thus increase plasma levels of 5-FU. Caution is advised as co-administration may increase the toxicity of Teysuno.

Coumarin-derivative anticoagulant

The activity of a coumarin-derivative anticoagulant was enhanced by Teysuno. Caution is advised as co-administration of Teysuno and coumarin anticoagulation therapy may increase the risk of bleeding (see section 4.4).

Phenytoin

Fluoropyrimidines may increase phenytoin plasma concentration when administered concomitantly with phenytoin causing phenytoin toxicity. Frequent monitoring of phenytoin blood/plasma levels is advised when Teysuno and phenytoin are administered concomitantly. If indicated, the dose of phenytoin should be adjusted according to the phenytoin SmPC. If phenytoin toxicity develops, appropriate measures should be taken.

Other

Based on non-clinical data, allopurinol may decrease anti-tumour activity due to suppression of phosphorylation of 5-FU. Therefore, concurrent administration with Teysuno should be avoided.

Other forms of interaction

Food

Administration of Teysuno with a meal reduced exposure to oteracil and gimeracil, with a more pronounced effect for oteracil than for gimeracil (see section 5.2). It should be taken with water at least 1 hour before or 1 hour after a meal (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with this medicinal product.

Contraception in males and females

Contraceptive measures must be taken by both male and female patients during and up to 6 months after stopping treatment with Teysuno.

Pregnancy

Teysuno is contraindicated in pregnancy (see section 4.3). There are no data from the use of Teysuno in pregnant women. Studies in animals have shown reproductive toxicity. As with other fluoropyrimidines, Teysuno administration caused embryoletality and teratogenicity in animals (see section 5.3). If the patient becomes pregnant while receiving Teysuno, treatment should be discontinued and the potential risk to the foetus must be explained. Genetic counseling should be considered.

Breastfeeding

Teysuno is contraindicated during breastfeeding (see section 4.3). It is not known whether Teysuno or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of Teysuno or its metabolites in milk (for details see section 5.3).

A risk to newborns/infants cannot be excluded. Breastfeeding should be discontinued while receiving treatment with Teysuno.

Fertility

No data are available on the effect of Teysuno in combination with cisplatin on human fertility. Non-clinical studies demonstrated that Teysuno did not appear to affect male or female fertility in the rat (see section 5.3).

Refer to the cisplatin SmPC for the effects of cisplatin on fertility, pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Teysuno has a moderate influence on the ability to drive and use machines as fatigue, dizziness, blurred vision, and nausea are common adverse reactions of Teysuno in combination with cisplatin.

4.8 Undesirable effects

Summary of safety profile

The overall safety profile of Teysuno in combination with cisplatin is based primarily on clinical study data from 593 patients with advanced gastric cancer treated with this regimen. In addition, there is post-marketing experience in over 866,000 Asian (mainly Japanese) patients.

Among 593 patients treated with Teysuno in combination with cisplatin, the most common severe adverse reactions (Grade 3 or higher with frequency of at least 10%) were neutropaenia, anaemia, and fatigue.

List of adverse reactions

The following headings are used to rank the adverse reactions by frequency: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available data). The frequencies of very common, common, and uncommon adverse reactions are from 593 patients treated with Teysuno in combination with cisplatin in clinical trials. The frequencies of medically relevant rare and very rare adverse reactions are estimated from post-marketing surveillance of 866,000 patients in Asia (mostly Japanese) treated with Teysuno-based therapy. Each term is presented in its most common category only and within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 7: Adverse reactions reported by decreasing seriousness in each frequency grouping

System Organ Class ^a	Very Common	Common	Uncommon	Rare / Very Rare
Infections and Infestations			Neutropenic sepsis, septic shock, sepsis, infection, pneumonia, bacteremia, respiratory tract infection, upper respiratory tract infection, pyelonephritis acute, urinary tract infection, pharyngitis, nasopharyngitis, rhinitis, tooth infection, candidiasis, oral herpes, paronychia, furuncle	
Neoplasms Benign, Malignant and Unspecified (Incl. cysts and polyps)			Tumour haemorrhage, cancer pain	
Blood and Lymphatic System Disorders	Neutropenia, leukopenia, anaemia, thrombocytopenia	Febrile neutropenia, lymphopenia	Pancytopenia, prothrombin time prolonged, international normalised ratio increased, hypoprothrombinaemia, prothrombin time shortened, granulocytosis, leukocytosis, eosinophilia, lymphocytosis, monocyte count decreased, monocyte count increased, thrombocythaemia	Disseminated intravascular coagulation
Immune System Disorders			Hypersensitivity	
Endocrine Disorders			Adrenal haemorrhage	
Metabolism and Nutrition Disorders	Anorexia	Dehydration, hypokalaemia, hyponatraemia, hypocalcaemia, hypomagnesaemia, hypoalbuminaemia, hyperkalaemia	Hyperglycaemia, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, hypophosphatemia, hypermagnesaemia, gout, hypoproteinaemia, hyperglobulinaemia, hyperlipidaemia, oral intake reduced	
Psychiatric Disorders		Insomnia	Confusional state, restlessness, personality disorder, hallucination, depression, anxiety, libido decreased, sexual inhibition	
Nervous System Disorders	Peripheral neuropathy	Dizziness, headache, dysgeusia	Cerebrovascular accident, cerebellar infarction, cerebrovascular disorder, convulsion, ischaemic stroke, syncope, hemiparesis, aphasia, ataxia, metabolic encephalopathy, loss of consciousness, acoustic neuritis, memory impairment, balance disorder, somnolence, tremor, ageusia, parosmia, burning sensation, formication	Leukoencephalopathy, anosmia
Eye Disorders		Vision disorder, lacrimal disorder, conjunctivitis, eye disorder	Eye allergy, eyelid ptosis, erythema of eyelid	Corneal erosion, corneal disorder

System Organ Class ^a	Very Common	Common	Uncommon	Rare / Very Rare
Ear and Labyrinth Disorders		Hearing impairment, deafness	Vertigo, ear congestion, ear discomfort	
Cardiac Disorders			Cardiac failure, acute myocardial infarction, pericardial effusion, atrial fibrillation, angina pectoris, cardiac fibrillation, tachycardia, palpitations	
Vascular Disorders		Hypotension, deep vein thrombosis, hypertension	Iliac artery thrombosis, hypovolaemic shock, arterial limb thrombosis, thrombosis, flushing, pelvic venous thrombosis, thrombophlebitis, phlebitis, phlebitis superficial, orthostatic hypotension, haematoma, hyperaemia, hot flush	
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea, epistaxis, hiccups, cough	Pulmonary embolism, respiratory tract haemorrhage, exertional dyspnoea, pharyngolaryngeal pain, rhinorrhoea, pharyngeal erythema, rhinitis allergic, dysphonia, productive cough, nasal congestion	Interstitial lung disease
Gastrointestinal Disorders	Diarrhoea, vomiting, nausea, constipation	Gastrointestinal haemorrhage, stomatitis, gastrointestinal inflammation, flatulence, abdominal pain, dysphagia, abdominal discomfort, dyspepsia, dry mouth	Gastrointestinal perforation, oesophagitis, gastrointestinal infection, ileus, gastrointestinal obstruction, ascites, lip oedema, oesophageal spasm, gastric ulcer, gastroesophageal reflux disease, reflux gastritis, retroperitoneal fibrosis, gastrointestinal disorder, anal haemorrhage, haemorrhoids, salivary hypersecretion, retching, salivary gland disorder, cheilitis, aerophagia, eructation, glossodynia, oral pain, teeth brittle	Acute pancreatitis
Hepatobiliary Disorders		Hyperbilirubinaemia, alanine aminotransferase increased, aspartate aminotransferase increased	Liver function test abnormal, gamma glutamyltransferase increased	Acute hepatic failure
Skin and Subcutaneous Tissue Disorders		Palmar-plantar erythrodysesthesia syndrome, rash, skin hyperpigmentation, dry skin, pruritus, alopecia,	Exfoliative rash, skin exfoliation, necrolytic migratory erythema, blood blister, dermatitis allergic, skin reaction, dermatitis acneiform, erythema, increased tendency to bruise, purpura, hyperhidrosis, night sweats, nail atrophy, pigmentation disorder, skin discoloration, hypertrichosis	Toxic epidermal necrolysis, Stevens-Johnson syndrome, photosensitivity reaction, nail disorder
Musculoskeletal and Connective Tissue Disorders		Musculoskeletal pain	Muscle spasms, arthralgia, pain in extremity, back pain, neck pain, bone pain, joint swelling, limb discomfort, muscle tightness, muscular weakness	Rhabdomyolysis
Renal and Urinary Disorders		Renal failure, blood creatinine increased, glomerular filtration rate decreased, blood urea increased	Toxic nephropathy, oligouria, haematuria, renal impairment, pollakiuria, blood creatine increased, blood creatinine decreased	
Reproductive System and Breast Disorders			Erectile dysfunction, breast tenderness, nipple pain	
General Disorders and Administration Site Conditions	Fatigue, asthenia	Mucosal inflammation, pyrexia, weight decreased, peripheral oedema, chills	Multi-organ failure, performance status decreased, pain, oedema, chest pain, chest discomfort, generalized oedema, face oedema, local swelling, localized oedema, weight increased, early satiety, feeling cold, injection site reaction, malaise	

System Organ Class ^a	Very Common	Common	Uncommon	Rare / Very Rare
Injury, Poisoning and Procedural Complications			Contusion, medication error	
^a Adverse reactions in the Investigations system organ class (SOC) have been reallocated to clinically appropriate SOC's related to their target organ. Different MedDRA preferred terms that were considered clinically similar have been grouped into a single term.				

Other clinical studies with Teysuno in combination with cisplatin

Although studies of Teysuno in combination with cisplatin that were conducted in Japan utilised doses and dosing schedules that differed from this regimen, the safety profile from these studies was similar, with the most common toxicities being haematologic, gastrointestinal, fatigue, and anorexia.

Paediatric population

No studies have been performed with Teysuno alone or in combination with cisplatin in paediatric patients.

Post-marketing surveillance experience in gastric cancer patients

The safety profile of Teysuno in a post-marketing safety surveillance study in Japan of 4,177 patients treated with Teysuno for advanced gastric cancer was generally similar to that seen with this regimen and in the Japanese registration studies (i.e., major toxicities were leukocytopenia, anorexia, and nausea/vomiting).

Description of selected adverse reactions

Ocular toxicity

Terms for treatment-related ocular toxicities have been combined as follows. The only Grade 3 or higher adverse reaction was reduced visual acuity.

- Vision disorder includes adverse reactions of blurred vision, diplopia, photopsia, reduced visual acuity, and blindness;
- Lacrimal disorder includes adverse reactions of increased lacrimation, dry eye, and acquired dacryostenosis;
- Eye disorder includes adverse reactions of eye pruritus, ocular hyperaemia, eye irritation, eye disorder, and foreign body sensation in eyes.

Neuropathy

Central and peripheral neuropathy has been reported in patients treated with Teysuno in combination with cisplatin. The term peripheral neuropathy includes the following reported adverse reactions: peripheral sensory neuropathy, paraesthesia, hypoaesthesia, peripheral neuropathy, polyneuropathy, neurotoxicity, and dysaesthesia.

Special populations

Elderly (see section 4.2)

Comparison of safety between 71 patients ≥ 70 years old (elderly) and 450 patients < 70 years old treated with Teysuno in combination with cisplatin in the FLAGS study demonstrated that the incidence of all Grade 3 or higher adverse reactions (62% vs 52%), all serious adverse reactions (30% vs 19%), and the rate of premature withdrawal due to adverse reactions from both Teysuno and cisplatin (21% vs 12%) appeared to be higher among patients ≥ 70 years old. A population pharmacokinetics analysis demonstrated that 5-FU exposure also tended to increase with age, but the

extent of the increase was within the range of individual variability. These changes with age were related to changes in renal function as measured by creatinine clearance (see section 5.2).

Gender

There were no clinically relevant differences in safety between males (N=382) and females (N=139) in the FLAGS study.

Patients with renal impairment (see sections 4.2, 4.3, 4.4, and 5.2)

Comparison of 218 patients with mild renal impairment at baseline (CrCl 51 to 80 ml/min) to 297 patients with normal renal function at baseline (CrCl >80 ml/min) treated with Teysuno in combination with cisplatin in the FLAGS study indicated that there were no clinically significant differences in safety between patients with mild renal impairment and patients with normal renal function.

In a study performed in patients with renal impairment, 7 patients with moderate renal impairment were treated with 20 mg/m² Teysuno. No dose limiting toxicities were observed and no dose reductions were needed among these patients. The most common adverse reactions were diarrhoea, nausea, and vomiting; no Grade 3 or higher adverse reactions were reported.

4.9 Overdose

The highest single dose of Teysuno taken was 1400 mg; this patient developed leukopenia (Grade 3). Manifestations of acute overdose reported include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation, bleeding, bone marrow depression, and respiratory failure. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

There is no known antidote available in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, antimetabolites, ATC code: L01BC53.

Mechanism of action

Teysono is an oral fluoropyrimidine anti-cancer medicinal product. It is a fixed dose combination of three active substances, tegafur, which after absorption is converted into the anti-cancer substance 5-FU; gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor to prevent degradation of 5-FU by the body; and, oteracil, an orotate phosphoribosyltransferase (OPRT) inhibitor that decreases the activity of 5-FU in normal gastrointestinal mucosa. The combination of tegafur, gimeracil, and oteracil was set at 1:0.4:1 molar ratio as optimum in order to maintain 5-FU exposure and thus sustain anti-tumour activity while reducing toxicity associated with 5-FU alone.

Tegafur is a prodrug of 5-FU with good oral bioavailability. Following oral administration, tegafur is gradually converted to 5-FU *in vivo*, mainly by CYP2A6 enzyme activity in the liver. 5-FU is metabolised by the liver enzyme DPD. 5-FU is activated within cells by phosphorylation to its active metabolite, 5-fluoro-deoxyuridine-monophosphate (FdUMP). FdUMP and reduced folate are bound to thymidylate synthase leading to formation of a ternary complex which inhibits DNA synthesis. In addition, 5-fluorouridine-triphosphate (FUTP) is incorporated into RNA causing disruption of RNA functions.

Gimeracil inhibits the metabolism of 5-FU by reversibly and selectively inhibiting DPD, the primary metabolic enzyme for 5-FU, so that higher plasma concentrations of 5-FU are achieved with the administration of a lower dose of tegafur.

After oral administration, oteracil was distributed at high concentrations in normal gastrointestinal tract tissues while considerably lower concentrations were seen in blood and tumour tissue in animal studies.

Pharmacodynamic effects

In a dose escalation study comparing the tolerability of 5-FU in Teysuno and tegafur + gimeracil (no oteracil), the 25 mg/m² dose level could not be attained in the absence of oteracil due to the occurrence of dose limiting toxicities (Grade 3 diarrhoea in 2 patients, and cardio-respiratory arrest in 1 patient) in the tegafur+gimeracil arm. The 5-FU pharmacokinetic profile was similar in the presence and absence of oteracil.

Mean 5-FU maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values were approximately 3-fold higher after Teysuno administration than after administration of tegafur alone, despite a 16-fold lower Teysuno dose (50 mg of tegafur) compared to tegafur alone (800 mg), and are attributed to inhibition of DPD by gimeracil. Maximum plasma uracil concentration was observed at 4 hours, with a return to baseline levels within approximately 48 hours after dosing, indicating the reversibility of the DPD inhibition by gimeracil.

A study of the effect of Teysuno on cardiac repolarisation conducted in advanced cancer patients met the definition for a negative study according to International Conference on Harmonisation (ICH) guidelines. No consistent relationship was seen between absolute QTcF interval values or change from Baseline values and maximum plasma concentration of Teysuno components.

A Phase I study established the current regimen by evaluating cohorts of Teysuno and cisplatin of 30 mg/m² and 60 mg/m² (dose-limiting toxicities [DLTs] seen were fatigue, and diarrhoea and dehydration); 25 mg/m² and 60 mg/m²; and 25 mg/m² and 75 mg/m². Despite the lack of DLTs in the last cohort, the dose of cisplatin was not elevated beyond 75 mg/m².

In the Phase III FLAGS study, there was no apparent relationship between 5-FU AUC (Teyuno/cisplatin arm) and 5-FU concentration (5-FU/cisplatin arm) during Cycle 1 and efficacy outcomes of overall survival (OS) or progression-free survival (PFS).

Advanced gastric cancer:

Data from a multicentre, multinational (excluding Asia), randomised, controlled, open-label Phase III clinical study (FLAGS) support the use of Teysuno in combination with cisplatin for the treatment of patients with advanced gastric cancer. In this study, 521 patients were randomised to treatment with Teysuno (25 mg/m² orally twice daily for 21 days followed by a 7-day rest period) and cisplatin (75 mg/m² intravenous infusion once every 4 weeks); and 508 patients were randomised to treatment with 5-FU (1000 mg/m²/24 hours as a continuous intravenous infusion on Days 1 through 5 repeated every 4 weeks) and cisplatin (100 mg/m² as an intravenous infusion on Day 1 repeated every 4 weeks). Patient characteristics are provided in Table 8.

Table 8: Demographics and baseline characteristics of patients in the FLAGS study

	Teysuno + Cisplatin 75 mg/m² (N=521)	5-FU + Cisplatin 100 mg/m² (N=508)
Gender, n (%)		
Male	382 (73)	347 (68)
Female	139 (27)	161 (32)
Age, years		
Median (Range)	59 (18-83)	60 (20-85)
≥65, n (%)	160 (31)	164 (32)
Race, n (%)		
White	447 (86)	438 (86)
Black or African American	5 (1.0)	7 (1.4)
Asian	4 (0.8)	4 (0.8)
American Indian or Alaska Native	4 (0.8)	6 (1.2)
Other	61 (12)	53 (10)
ECOG Performance Status, n (%)		
0	226 (43)	200 (39)
1	295 (57)	308 (61)
Location of primary lesion, n (%)		
Stomach	438 (84)	417 (82)
Gastro-oesophageal junction	82 (16)	88 (17)
Both	1 (0.2)	3 (0.6)
Metastatic disease, n (%)		
≥2 metastatic sites	497 (95)	488 (96)
	340 (65)	327 (64)

For the primary endpoint of overall survival, Teysuno in combination with cisplatin was non-inferior to 5-FU in combination with cisplatin (see Table 9). At the time of primary analysis, the median follow-up for overall survival in the full analysis set was 18.3 months.

Table 9: Overall survival and progression-free survival in FLAGS

Endpoint	Teysuno + Cisplatin		5-FU + Cisplatin		Hazard Ratio [95% CI]
	N	Median [95% CI], months	N	Median [95% CI], months	
Overall Survival					
Intent-to-treat	527	8.5 [7.9, 9.3]	526	7.9 [7.2, 8.5]	0.94 [0.82, 1.07]
Full analysis set	521	8.6 [7.9, 9.5]	508	7.9 [7.2, 8.5]	0.92 [0.80, 1.05]
Progression-free Survival					
Full analysis set	521	4.8 [4.0, 5.5]	508	5.5 [4.4, 5.8]	0.99 [0.86, 1.14]

CI = confidence interval; Full analysis set = all randomised, treated patients analysed as allocated (primary analysis population)

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Teysuno in all subsets of the paediatric population in gastric adenocarcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The single and multiple dose pharmacokinetics (PK) of Teysuno in combination with cisplatin were evaluated in three studies. Eighteen additional PK studies were performed using the relevant regimen as monotherapy. All studies were performed in cancer patients.

Absorption

After administration of a single dose of 50 mg Teysuno (expressed as tegafur content) in man (approximately 30 mg/m² based on body surface area of 1.56 to 2.10 m² for a typical patient; N=14), the median T_{max} for Teysuno components tegafur, gimeracil, and oteracil was 0.5, 1.0, and 2.0 hours, respectively, and the mean ± standard deviation (SD) AUC_{0-inf} and C_{max} was 14595 ± 4340 ng.hr/ml and 1762 ± 279 ng/ml for tegafur, 1884 ± 640 ng.hr/ml and 452 ± 102 ng/ml for gimeracil, 556 ± 281 ng.hr/ml and 112 ± 52 ng/ml for oteracil. The median T_{max} for 5-FU was 2.0 hours and the mean AUC_{0-inf} and C_{max} was 842 ± 252 ng.hr/ml and 174 ± 58 ng/ml. Levels of tegafur, gimeracil, oteracil and 5-FU were quantifiable through 10 hours postdose. After administration of 30 mg/m² doses, steady-state conditions are reached for tegafur, gimeracil, and oteracil at the latest by Day 8.

After multiple dose administration (30 mg/m², expressed as tegafur content, twice daily for 14 days; N=10), the median T_{max} of tegafur, gimeracil, and oteracil was 0.8, 1.0, and 2.0 hours, respectively, and the corresponding mean ± SD AUC_(0-12h) and C_{max} was 19967 ± 6027 ng.hr/ml and 2970 ± 852 ng/ml for tegafur, 1483 ± 527 ng.hr/ml and 305 ± 116 ng/ml for gimeracil, and 692 ± 529 ng.hr/ml and 122 ± 82 ng/ml for oteracil. The median T_{max} for 5-FU was 2.0 hours and the mean AUC_(0-12h) and C_{max} was 870 ± 405 ng.hr/ml and 165 ± 62 ng/ml, respectively.

Administration of Teysuno under fed conditions resulted in decreased AUC_{0-inf} for oteracil of approximately 71% and gimeracil of approximately 25% relative to fasting administration. Concomitant administration of a proton pump inhibitor (PPI) reduced the effect of food on the pharmacokinetic profile of oteracil, but not by a sufficient margin to completely negate the food effect. There was a 15% decrease in AUC_{0-inf} for 5-FU under fed versus fasting conditions, and tegafur exposure was not altered by food (thus demonstrating absence of a food effect).

Mean AUC_{0-inf} and C_{max} for 5-FU were approximately 3-fold greater following administration of Teysuno (50 mg expressed as tegafur content) than following administration of tegafur alone (800 mg), while AUC_{0-inf} and C_{max} values for the 5-FU metabolite α-fluoro-β-alanine (FBAL) were approximately 15- to 22-fold lower following administration of Teysuno than following administration of tegafur.

The oteracil component of Teysuno did not affect the pharmacokinetic profiles of 5-FU, tegafur, gimeracil, FBAL, or uracil. The gimeracil component did not affect the pharmacokinetic profile of tegafur.

Distribution

Oteracil, gimeracil, 5-FU, and tegafur were 8.4%, 32.2%, 18.4%, and 52.3% protein bound, respectively. The protein binding in human serum was not concentration-dependent over a range of 0.1 to 1.0 µg/ml for oteracil, gimeracil, and 5-FU and 1.2 to 11.8 µg/ml for tegafur.

There are no clinical data on the distribution of radiolabeled components of Teysuno. Although no intravenous data are available for Teysuno in humans, the volume of distribution could be roughly estimated from the apparent volume of distribution and urinary excretion data as 16 l/m², 17 l/m², and 23 l/m² for tegafur, gimeracil and oteracil, respectively.

Biotransformation

The main metabolic pathway for tegafur is through conversion to 5-FU via CYP2A6 in the liver, whereas gimeracil was stable in human liver homogenate (S9 fraction) with adenosine 3'-phosphate 5'-phosphosulphate lithium salt (PAPS; a co-factor for sulfotransferase) or nicotinamide adenine dinucleotide phosphate (NADPH). Based on the results of *in vitro* studies, a part of oteracil is non-enzymatically degraded to 5-azauracil (5-AZU) by gastric fluid, and is then converted to cyanuric acid (CA) in the digestive tract. 5-AZU and CA do not inhibit OPRT enzyme activity. Only a small amount of oteracil is metabolised in the liver because of its low permeability.

In vitro evaluation using human liver microsomes indicated that neither tegafur, gimeracil nor oteracil showed any relevant inhibitory effects on enzyme activities of the cytochrome P450 isoforms tested (i.e., CYP1A1/2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4).

In vitro evaluation using primary cultures of human hepatocytes indicated that tegafur (0.7-70 μM), gimeracil (0.2-25 μM) and oteracil (0.04-4 μM) had little or no inductive effect on CYP1A2, CYP2B6 or CYP3A4/5 metabolic activities.

Using plasma uracil concentrations to assess DPD activity in clinical studies, no marked changes in plasma uracil concentrations were observed after administration of a single 800 mg dose of tegafur while plasma uracil concentrations increased markedly after administration of a single 50 mg dose of Teysuno (reflecting DPD inhibition by gimeracil). Following both single dose (50 mg) and multiple dose (30 mg/m^2 twice daily) administration of Teysuno in man, maximum uracil concentrations reflecting DPD inhibition were observed approximately 4 hours postdose. Similar inhibition was seen following single and multiple dosing. The plasma concentrations of uracil returned to baseline levels approximately 48 hours after dosing indicating reversibility of DPD inhibition by gimeracil.

Elimination

In man, the apparent terminal elimination half-life ($T_{1/2}$) of 5-FU observed after administration of Teysuno (containing tegafur, a 5-FU prodrug) was longer (approximately 1.6 - 1.9 hours) than that previously reported after intravenous administration of 5-FU (10 to 20 minutes). Following a single dose of Teysuno, $T_{1/2}$ values ranged from 6.7 to 11.3 hours for tegafur, from 3.1 to 4.1 hours for gimeracil, and from 1.8 to 9.5 hours for oteracil.

Following a single dose of Teysuno, approximately 3.8% to 4.2% of administered tegafur, 65% to 72% of administered gimeracil, and 3.5% to 3.9% of administered oteracil were excreted unchanged in the urine. Among the metabolites, 9.5% to 9.7% of the administered tegafur was excreted in the urine as 5-FU and approximately 70% to 77% as FBAL, accounting for approximately 83% to 91% of the administered Teysuno dose (total tegafur + 5-FU + FBAL). There was no effect of gimeracil on renal clearance of tegafur, FBAL, and 5-FU following administration of Teysuno as compared to their clearance following administration of tegafur alone.

Linearity/non-linearity

In a Japanese Phase I study that utilized 5 dose groups with doses ranging from 25 to 200 mg/body , there was a dose-proportional increase in exposure for tegafur, gimeracil and oteracil. However, the increase in 5-FU exposure tended to be greater than proportional to the increasing tegafur dose.

Pharmacokinetics in special populations

Population PK

A population PK analysis of Teysuno components and metabolites assessed the influence of various factors, including gender, age, food, ethnicity (Caucasian vs Asian), renal function, and hepatic function in 315 patients. Renal function, as reflected by creatinine clearance, was the primary factor that influenced gimeracil exposure and 5-FU exposure. As renal function decreased, there was an increase in 5-FU steady state exposure. This analysis also demonstrated that the trend in changes in Teysuno pharmacokinetics observed with increasing age was related to change in renal function as measured by creatinine clearance.

Renal impairment

In a Phase I Teysuno monotherapy study that investigated the pharmacokinetics of components and metabolites in patients with normal and impaired renal function, patients with mild renal impairment (CrCl 51 to 80 ml/min) receiving the same monotherapy dose of 30 mg/m^2 twice daily (the maximum tolerated dose for monotherapy) as patients with normal renal function (CrCl >80 ml/min) had an

increase in mean 5-FU AUC_{0-inf} relative to that of the normal patients. Patients with moderate renal impairment (CrCl 30 to 50 ml/min) who received a reduced dose of 20 mg/m² twice daily showed no significant increase in mean 5-FU AUC_{0-inf} relative to that of the normal group. The increase in 5-FU exposure in patients with mild renal impairment in this study together with the results of simulation in the population pharmacokinetic analysis suggest that a Teysuno dose of 25 mg/m² twice daily in patients with mild renal impairment could achieve 5-FU plasma concentrations similar to those obtained in patients with normal renal function receiving 30 mg/m² twice daily as monotherapy and also those with moderate renal impairment receiving 20 mg/m² twice daily.

Hepatic impairment

There were no significant differences in AUCs of 5-FU, tegafur, gimeracil, or oteracil after either single or multiple dose administration of Teysuno 30 mg/m² twice daily in patients with mild, moderate, or severe hepatic impairment compared to those with normal hepatic function. After single dose administration, there was a statistically significant decrease in 5-FU and gimeracil C_{max} for the severe hepatic impairment group relative to that of the normal group, but this difference was not observed after multiple dose administration.

Ethnic differences

A Phase I study investigated the pharmacokinetics of Teysuno monotherapy in Asian (Chinese/Malay) and Caucasian (US) patients. Consistent with the lower CYP2A6 activity in the Asian patients, tegafur AUC_{0-12} was higher and $T_{1/2}$ was longer in the Asian group compared to the Caucasian group. Gimeracil and uracil AUC_{0-12} values were comparable between the two groups, suggesting that DPD inhibition was similar for the Asian and Caucasian groups. Exposure of 5-FU was not statistically significantly different between the two groups. Oteracil AUC_{0-12} in the Asian group was approximately half that of the Caucasian group, however, this difference was not statistically significant due to its large individual variability.

Studies in Japanese patients have suggested an effect of CYP2A6*4 polymorphism on Teysuno pharmacokinetics. Although CYP2A6 variants are associated with pharmacokinetic variability of tegafur, the AUC of gimeracil, which is affected by renal function, is the key determinant in the pharmacokinetic variability of 5-FU. In the Phase III (FLAGS) study, tegafur AUC was significantly higher in patients with the CYP2A6*4 allele, however, no significant difference was found for 5-FU AUC and for the incidence of adverse reactions. Therefore, the CYP2A6 polymorphism differences between Asian and Western populations do not appear to be the key determinant for differences in the MTD between populations. However, limited data available on CYP2A6*4/*4 genotype in Japanese patients treated with Teysuno suggest significantly decreased 5-FU levels in this subpopulation. No dose advice for this subpopulation can be provided. This CYP2A6*4 allele is uncommon in the Caucasian population.

Paediatric population

No pharmacokinetic studies have been conducted with Teysuno in paediatric patients.

5.3 Preclinical safety data

Repeat-dose toxicity studies in rats, dogs and monkeys produced changes typically associated with administration of an anti-cancer medicinal product eliciting cytotoxic effects on populations of rapidly dividing cells, such as anaemia, decrease in the immune and digestive system function, disruption of spermatogenesis, and atrophy in male and female reproductive organs.

Treatment with Teysuno produced various skin effects in rat (keratosis of footpad and tail) and dog (skin crusts and erosions). In addition, hyperpigmentation in the skin and eyes and corneal opacity in dogs and cataracts in rats were observed following repeat dosing. These changes were reversible.

Teysuno does not appear to affect male or female fertility in the rat; however, administration at any time after conception resulted in a range of external, visceral, and skeletal foetal abnormalities in rat and rabbit. There is therefore a high risk for developmental toxicity at clinical doses, primarily due to tegafur (5-FU) and to oteracil to a lesser extent.

Teysuno was not carcinogenic in either the rat or the mouse. Teysuno was not found to be mutagenic when tested in the *in vitro* Ames assay. Teysuno was clastogenic *in vitro* using Chinese hamster lung cells and was weakly clastogenic *in vivo* in mouse bone marrow.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Lactose monohydrate

Magnesium stearate

Capsule shell

Gelatin

Titanium dioxide (E171)

Sodium lauryl sulphate

Talc

Ink

Red iron oxide (E172)

Yellow iron oxide (E172)

FD&C Blue No. 2 aluminium lake (E132)

Carnauba wax

Bleached shellac

Glyceryl monooleate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PCTFE/PVC/Al opaque blisters containing either 42 capsules (3 blisters containing 14 capsules each) or 84 capsules (6 blisters containing 14 capsules each).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Hands should be washed after handling capsules.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Taiho Pharma Europe, Limited
55 Colmore Row, Birmingham
West Midlands, B3 2AS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Brecon Pharmaceuticals Ltd.
Wye Valley Business Park
Brecon Road - Hay-on-Wye
Herford, HR3 5PG
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **Conditions or restrictions with regard to the safe and effective use of the medicinal product**

Not applicable

- **Other conditions**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.4 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA

ANNEX III
LABELLING AND PAGKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Teysuno 15 mg/4.35 mg/11.8 mg hard capsules
tegafur/gimeracil/oteracil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 15 mg tegafur, 4.35 mg gimeracil and 11.8 mg oteracil (as 14.7 mg of monopotassium salt).

3. LIST OF EXCIPIENTS

Also contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

42 capsules

126 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Taiho Pharma Europe, Limited, 55 Colmore Row, Birmingham, West Midlands, B3 2AS, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Teysuno 15mg/4.35 mg/11.8 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Teysuno 15 mg/4.35 mg/11.8 mg capsules
tegafur/gimeracil/oteracil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Taiho Pharma Europe, Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Teysuno 20 mg/5.8 mg/15.8 mg hard capsules
tegafur/gimeracil/oteracil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 20 mg tegafur, 5.8 mg gimeracil and 15.8 mg oteracil (as 19.6 mg of monopotassium salt).

3. LIST OF EXCIPIENTS

Also contains lactose.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

42 capsules

84 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Taiho Pharma Europe, Limited, 55 Colmore Row, Birmingham, West Midlands, B3 2AS, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Teysuno 20mg/5.8 mg/15.8 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Teysuno 20 mg/5.8 mg/15.8 mg capsules
tegafur/gimeracil/oteracil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Taiho Pharma Europe, Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Teysuno 15 mg/4.35 mg/11.8 mg hard capsules Tegafur/gimeracil/oteracil

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Teysuno is and what it is used for
2. Before you take Teysuno
3. How to take Teysuno
4. Possible side effects
5. How to store Teysuno
6. Further information

1. WHAT TEYSUNO IS AND WHAT IT IS USED FOR

Teysuno belongs to the fluoropyrimidine class of medicine known as “antineoplastic agents” which stop the growth of cancer cells.

Teysuno is prescribed by doctors for the treatment of adults with advanced stomach (gastric) cancer and is taken with cisplatin, another anti-cancer medicine.

2. BEFORE YOU TAKE TEYSUNO

Do not take Teysuno if you:

- are allergic (hypersensitive) to tegafur, gimeracil, oteracil or any of the other ingredients of Teysuno
- are taking other fluoropyrimidine anti-cancer medicine such as fluorouracil and capecitabine, or have had severe and unexpected reactions to fluoropyrimidines
- have known genetic deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)
- are pregnant or breastfeeding
- have severe blood disorders
- have severe kidney problems
- are currently being treated or have been treated in the last 4 weeks with sorivudine, brivudine or a similar class of anti-viral medicines

Take special care with Teysuno

- Before treatment with Teysuno, tell your doctor if you have:
 - blood disorders
 - kidney disease
 - stomach and/or bowel problems such as pain, diarrhoea, vomiting and dehydration
 - eye disorders, such as “dry eye” or increased tearing
- Teysuno is not recommended for children under 18 years of age.
- Teysuno cannot be substituted for other oral fluoropyrimidine medicine.

Taking other medicines

Before starting treatment, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is extremely important, as taking more than one medicine at the same time can strengthen or weaken the effect of the medicines. You need to be particularly careful if you are taking any of the following:

- other fluoropyrimidine based medicines such as the anti-fungal flucytosine
- antivirals such as brivudine or sorivudine
- inhibitors of the enzyme CYP2A6 which activates Teysuno such as tranlycypromine and methoxsalen
- folic acid (often used in chemotherapy with methotrexate)
- blood-thinning medicines: coumarin-derivative anticoagulants such as warfarin
- medicines for the treatment of seizures or tremors such as phenytoin
- medicines that treat gout such as allopurinol

Taking Teysuno with food and drink

Teysono should be taken at least one hour before or one hour after a meal.

Pregnancy and breastfeeding

Before starting treatment, you must tell your doctor or pharmacist if you are pregnant, if you think you are pregnant, or if you intend to become pregnant. You must not take Teysuno if you are pregnant or think you might be.

During and up to 6 months after treatment with Teysuno, you must use contraceptive measures. If you become pregnant during this time, you must tell your doctor.

You must not breastfeed if you are taking Teysuno.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Use caution when driving or operating a machine, as Teysuno may make you tired, nauseous or have blurred vision. If you have any doubts talk to your doctor.

Important information about some of the ingredients of Teysuno

This medicine contains **lactose** (one type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE TEYSUNO

Always take Teysuno exactly as your doctor has told you. You should check with your doctor if you are not sure.

Your doctor will tell you what dose you need to take, when to take it and for how long you need to take it. Your dose of Teysuno will be determined by your doctor based on your height and weight. Your doctor may reduce the dose if you have side effects that are too severe.

Teysono capsules should be swallowed with water at least 1 hour before or 1 hour after a meal. Teysuno must be taken twice daily (morning and evening).

Teysono capsules are usually taken for 21 days followed by a 7 day rest period (when no capsules are taken). This 28 day period is one treatment cycle. The cycles are repeated.

Teysono will be given with another anti-cancer medicine called cisplatin. Cisplatin will be stopped after 6 treatment cycles. Teysuno can be continued after stopping cisplatin.

If you take more Teysuno than you should

If you take more capsules than you should, contact your doctor immediately.

If you forget to take Teysuno

Do not take the missed dose at all and do not double the next one. Instead, continue your regular dosing schedule and check with your doctor.

If you stop taking Teysuno

There are no side effects caused by stopping treatment with Teysuno. In case you are using blood thinning or anti-seizure medications, stopping Teysuno might require that your doctor adjusts the dose of your medications.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Teysuno can cause side effects, although not everybody gets them. While some symptoms are easily identified as side effects by the patients themselves, a blood test is required to identify some other symptoms. Your doctor will discuss this with you and will explain the possible risks and benefits of the treatment.

If you are concerned about the side effects below, talk to your doctor.

Very common side effects (affect more than 1 user in 10) include:

- **Diarrhoea, nausea, vomiting, constipation**
 - o If you experience diarrhoea more than 4 times a day or in the middle of the night, or if you experience sore mouth accompanied by diarrhoea, **stop taking Teysuno and contact your doctor immediately.**
 - o If you experience diarrhoea, avoid high-fibre, fatty and spicy foods.
 - o Take plenty of liquids between meals to replace lost fluids and prevent dehydration, low blood volume, and imbalance of salts or chemicals in the blood.
 - o If you experience nausea and vomit a dose of medication, make sure you tell your doctor. Do not replace the dose that has been vomited.
 - o If you vomit more than two times in 24 hours, **stop taking Teysuno and contact your doctor immediately.**
 - o To help manage nausea and vomiting:
 - Lie down or take deep breaths when feeling nauseous
 - Avoid tight clothing
- **Low red blood cell count** leading to anaemia
 - o You may have symptoms such as cold hands and feet, looking pale, light-headedness, fatigue, breathlessness.
 - o If you experience any of the above-mentioned symptoms, try not to work too hard and get ample sleep and rest.
- **Low white blood cell count** leading to increased risk of severe local (e.g., oral, lung, urine) or blood infections
 - o You may have symptoms such as fever, chills, coughing, sore throat.
 - o If you have fever of 38.5° C or higher, **stop taking Teysuno and contact your doctor immediately.**
 - o To prevent infection, keep away from crowded places, gargle upon returning home, and wash your hands before meals and before and after using the bathroom.
- **Low platelet count** leading to an increased chance of bleeding
 - o If you have bleeding of the skin, mouth (caused by brushing teeth), nose, respiratory tract, stomach, gut, etc., **stop taking Teysuno and contact your doctor immediately.**
 - o To prevent bleeding, avoid hard work or strenuous sports so as to prevent injuries and bruises. Wear loose clothing to protect the skin. Brush your teeth and blow your nose gently.
- **Loss of appetite (anorexia)** can lead to weight loss and dehydration

- You may become dehydrated if you do not eat and/or drink enough water.
- If you become dehydrated you may have symptoms such as dry mouth, weakness, dry skin, dizziness, cramping
- Try to eat frequent small meals. Avoid fatty and strong-smelling food. Even if you do not feel hungry, continue to eat as much as you can to maintain good nutrition.
- If you feel tired and have fever together with loss of appetite, contact your doctor immediately.
- **Nerve disorder:** you may feel numbness, tingling, pain, abnormal sensation, weak muscle, shaking, or movement difficulties.
- **Weakness and fatigue**, which could be side effects caused by other medicines.

Common side effects (affect 1 to 10 users in 100) include:

- **Nerve:** headache, dizziness, sleeplessness, changes in taste
- **Eye:** eye problems, increased or decreased tearing discomfort, vision problems
- **Ear:** hearing problems
- **Blood vessels:** high or low blood pressure, blood clots in the leg and lung
- **Lung and nasal passages:** shortness of breath, cough
- **Gut and mouth:** dry mouth, sores in mouth, throat, and oesophagus, hiccups, abdominal pain, indigestion, stomach or bowel inflammation, perforation of the stomach, small intestine, and large bowel.
- **Liver:** yellow eyes and skin, changes in blood tests which show the way the liver is working,
- **Skin:** hair loss, itchiness, rash or dermatitis, skin reaction, dry skin, hand-and-foot reaction (pain, swelling and redness of hands and/or feet), pigmented skin patches
- **Kidney:** decreased urine volume, changes in blood tests which show the way the kidney is working, kidney impairment and failure
- **Other:** chills, weight decrease, swelling in specific areas and muscle bone pain

Uncommon side effects (affect 1 to 10 users in 1,000) include:

- **Mental:** seeing and hearing some things that are not there, personality change, unable to sit still, confusion, feeling of nervousness, depression, sexual dysfunction
- **Nerve:**, voice disorder, inability to speak and understand words, memory problem, unsteady gait, balance problems, one sided body weakness, sleepiness, nerve inflammation, distorted sense of smell, brain dysfunction, fainting, loss of consciousness, stroke, seizures
- **Eye:** itchy and red eyes, allergic reactions in eyes, drooping upper eyelid
- **Ear:** vertigo, ear clogging, ear discomfort
- **Heart:** irregular or fast heart beat, chest pain, accumulation of excess fluid around the heart, heart attack, heart failure
- **Blood vessels:** inflammation of a vein, hot flush
- **Lung and nasal passages:** runny nose, voice disorder, nasal clogging, pharyngeal erythema, hay fever
- **Gut and mouth:** fluid in the abdomen, gastroesophageal reflux disease, increased salivary secretion, excessive burping and belching, lip inflammation, gastrointestinal disorder, oral pain, abnormal contractions of muscles of the oesophagus, blockage in the stomach and intestine, stomach ulcer, retroperitoneal fibrosis, teeth that crack or break easily, swallowing difficulty, disorder of the salivary gland, haemorrhoids
- **Skin:** loss of skin colour, peeling skin, excessive body hair, nail shrinkage, excessive sweating,
- **General:** general condition worsening, weight increase, redness and swelling at the injection site, cancer pain and bleeding, multiple organ failure
- **Changes in blood tests:** high blood sugar, high blood lipids, changes in blood clotting time, high blood cell counts, low or high protein level
- **Other:** frequent urination, blood in urine, neck pain, back pain, breast pain, muscle tightness or cramps, joint swelling, limb discomfort, muscle weakness, arthritis inflammation and pain

Rare side effects (affect 1 to 10 users in 10,000) and very rare side effects (affect less than 1 user in 10,000) include:

- acute liver failure
- pancreas infection
- muscle breakdown
- loss of sense of smell
- sun allergy
- loss of a portion of the surface “skin” of the eye (corneal erosion)
- widespread blood clotting and bleeding
- disease affecting the white matter of the brain
- serious illness with blistering of the skin, mouth, eyes, and genitals

If you experience any of the side effects or if you notice any side effects not listed in this leaflet, please tell your doctor.

If any of the side effects get serious, stop taking Teysuno and tell your doctor immediately.

5. HOW TO STORE TEYSUNO

- Keep out of the reach and sight of children.
- Do not use Teysuno after the expiry date which is stated on the outer carton and blister after EXP. The expiry date refers to the last day of the month.
- This medicine does not require any special storage conditions.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Teysuno contains

- The active substances are tegafur, gimeracil and oteracil. Each hard capsule contains 15 mg tegafur, 4.35 mg gimeracil, and 14.7 mg oteracil monopotassium corresponding to 11.8 mg oteracil.
- The other ingredients are:

Capsule contents: lactose monohydrate, magnesium stearate

Capsule shell: gelatin, red iron oxide (E172), titanium dioxide (E171), sodium lauryl sulphate, talc

Ink: red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminium lake (E132), carnauba wax, bleached shellac, glyceryl monooleate

What Teysuno looks like and contents of the pack

The hard capsules have a white body and opaque brown cap imprinted "TC448" in grey.

Each pack contains either 42 capsules (3 blisters of 14 capsules each) or 126 capsules (9 blisters of 14 capsules each)

Marketing Authorisation Holder

Taiho Pharma Europe, Limited
55 Colmore Row, Birmingham
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Manufacturer

Brecon Pharmaceuticals Ltd.
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Hay-on-Wye
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This leaflet was last approved in

Detailed information this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu> . There are also links to other websites about rare diseases and treatments.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Teysuno 20 mg/5.8 mg/15.8 mg hard capsules Tegafur/gimeracil/oteracil

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Teysuno is and what it is used for
2. Before you take Teysuno
3. How to take Teysuno
4. Possible side effects
5. How to store Teysuno
6. Further information

1. WHAT TEYSUNO IS AND WHAT IT IS USED FOR

Teysuno belongs to the fluoropyrimidine class of medicine known as “antineoplastic agents” which stop the growth of cancer cells.

Teysuno is prescribed by doctors for the treatment of adults with advanced stomach (gastric) cancer and is taken with cisplatin, another anti-cancer medicine.

2. BEFORE YOU TAKE TEYSUNO

Do not take Teysuno if you:

- are allergic (hypersensitive) to tegafur, gimeracil, oteracil or any of the other ingredients of Teysuno
- are taking other fluoropyrimidine anti-cancer medicine such as fluorouracil and capecitabine, or have had severe and unexpected reactions to fluoropyrimidines
- have known genetic deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)
- are pregnant or breastfeeding
- have severe blood disorders
- have severe kidney problems
- are currently being treated or have been treated in the last 4 weeks with sorivudine, brivudine or a similar class of anti-viral medicines

Take special care with Teysuno

- Before treatment with Teysuno, tell your doctor if you have:
 - blood disorders
 - kidney disease
 - stomach and/or bowel problems such as pain, diarrhoea, vomiting and dehydration
 - eye disorders, such as “dry eye” or increased tearing
- Teysuno is not recommended for children under 18 years of age.
- Teysuno cannot be substituted for other oral fluoropyrimidine medicine.

Taking other medicines

Before starting treatment, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is extremely important, as taking more than one medicine at the same time can strengthen or weaken the effect of the medicines. You need to be particularly careful if you are taking any of the following:

- other fluoropyrimidine based medicines such as the anti-fungal flucytosine
- antivirals such as brivudine or sorivudine
- inhibitors of the enzyme CYP2A6 which activates Teysuno such as tranlycypromine and methoxsalen
- folic acid (often used in chemotherapy with methotrexate)
- blood-thinning medicines: coumarin-derivative anticoagulants such as warfarin
- medicines for the treatment of seizures or tremors such as phenytoin
- medicines that treat gout such as allopurinol

Taking Teysuno with food and drink

Teysono should be taken at least one hour before or one hour after a meal.

Pregnancy and breastfeeding

Before starting treatment, you must tell your doctor or pharmacist if you are pregnant, if you think you are pregnant, or if you intend to become pregnant. You must not take Teysuno if you are pregnant or think you might be.

During and up to 6 months after treatment with Teysuno, you must use contraceptive measures. If you become pregnant during this time, you must tell your doctor.

You must not breastfeed if you are taking Teysuno.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Use caution when driving or operating a machine, as Teysuno may make you tired, nauseous or have blurred vision. If you have any doubts talk to your doctor.

Important information about some of the ingredients of Teysuno

This medicine contains **lactose** (one type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE TEYSUNO

Always take Teysuno exactly as your doctor has told you. You should check with your doctor if you are not sure.

Your doctor will tell you what dose you need to take, when to take it and for how long you need to take it. Your dose of Teysuno will be determined by your doctor based on your height and weight. Your doctor may reduce the dose if you have side effects that are too severe.

Teysono capsules should be swallowed with water at least 1 hour before or 1 hour after a meal. Teysuno must be taken twice daily (morning and evening).

Teysono capsules are usually taken for 21 days followed by a 7 day rest period (when no capsules are taken). This 28 day period is one treatment cycle. The cycles are repeated.

Teysono will be given with another anti-cancer medicine called cisplatin. Cisplatin will be stopped after 6 treatment cycles. Teysuno can be continued after stopping cisplatin.

If you take more Teysuno than you should

If you take more capsules than you should, contact your doctor immediately.

If you forget to take Teysuno

Do not take the missed dose at all and do not double the next one. Instead, continue your regular dosing schedule and check with your doctor.

If you stop taking Teysuno

There are no side effects caused by stopping treatment with Teysuno. In case you are using blood thinning or anti-seizure medications, stopping Teysuno might require that your doctor adjusts the dose of your medications.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Teysuno can cause side effects, although not everybody gets them. While some symptoms are easily identified as side effects by the patients themselves, a blood test is required to identify some other symptoms. Your doctor will discuss this with you and will explain the possible risks and benefits of the treatment.

If you are concerned about the side effects below, talk to your doctor.

Very common side effects (affect more than 1 user in 10) include:

- **Diarrhoea, nausea, vomiting, constipation**
 - o If you experience diarrhoea more than 4 times a day or in the middle of the night, or if you experience sore mouth accompanied by diarrhoea, **stop taking Teysuno and contact your doctor immediately.**
 - o If you experience diarrhoea, avoid high-fibre, fatty and spicy foods.
 - o Take plenty of liquids between meals to replace lost fluids and prevent dehydration, low blood volume, and imbalance of salts or chemicals in the blood.
 - o If you experience nausea and vomit a dose of medication, make sure you tell your doctor. Do not replace the dose that has been vomited.
 - o If you vomit more than two times in 24 hours, **stop taking Teysuno and contact your doctor immediately.**
 - o To help manage nausea and vomiting:
 - Lie down or take deep breaths when feeling nauseous
 - Avoid tight clothing
- **Low red blood cell count** leading to anaemia
 - o You may have symptoms such as cold hands and feet, looking pale, light-headedness, fatigue, breathlessness.
 - o If you experience any of the above-mentioned symptoms, try not to work too hard and get ample sleep and rest.
- **Low white blood cell count** leading to increased risk of severe local (e.g., oral, lung, urine) or blood infections
 - o You may have symptoms such as fever, chills, coughing, sore throat.
 - o If you have fever of 38.5° C or higher, **stop taking Teysuno and contact your doctor immediately.**
 - o To prevent infection, keep away from crowded places, gargle upon returning home, and wash your hands before meals and before and after using the bathroom.
- **Low platelet count** leading to an increased chance of bleeding
 - o If you have bleeding of the skin, mouth (caused by brushing teeth), nose, respiratory tract, stomach, gut, etc., **stop taking Teysuno and contact your doctor immediately.**
 - o To prevent bleeding, avoid hard work or strenuous sports so as to prevent injuries and bruises. Wear loose clothing to protect the skin. Brush your teeth and blow your nose gently.
- **Loss of appetite (anorexia)** can lead to weight loss and dehydration

- You may become dehydrated if you do not eat and/or drink enough water.
- If you become dehydrated you may have symptoms such as dry mouth, weakness, dry skin, dizziness, cramping
- Try to eat frequent small meals. Avoid fatty and strong-smelling food. Even if you do not feel hungry, continue to eat as much as you can to maintain good nutrition.
- If you feel tired and have fever together with loss of appetite, contact your doctor immediately.
- **Nerve disorder:** you may feel numbness, tingling, pain, abnormal sensation, weak muscle, shaking, or movement difficulties.
- **Weakness and fatigue,** which could be side effects caused by other medicines.

Common side effects (affect 1 to 10 users in 100) include:

- **Nerve:** headache, dizziness, sleeplessness, changes in taste
- **Eye:** eye problems, increased or decreased tearing discomfort, vision problems
- **Ear:** hearing problems
- **Blood vessels:** high or low blood pressure, blood clots in the leg and lung
- **Lung and nasal passages:** shortness of breath, cough
- **Gut and mouth:** dry mouth, sores in mouth, throat, and oesophagus, hiccups, abdominal pain, indigestion, stomach or bowel inflammation, perforation of the stomach, small intestine, and large bowel.
- **Liver:** yellow eyes and skin, changes in blood tests which show the way the liver is working,
- **Skin:** hair loss, itchiness, rash or dermatitis, skin reaction, dry skin, hand-and-foot reaction (pain, swelling and redness of hands and/or feet), pigmented skin patches
- **Kidney:** decreased urine volume, changes in blood tests which show the way the kidney is working, kidney impairment and failure
- **Other:** chills, weight decrease, swelling in specific areas and muscle bone pain

Uncommon side effects (affect 1 to 10 users in 1,000) include:

- **Mental:** seeing and hearing some things that are not there, personality change, unable to sit still, confusion, feeling of nervousness, depression, sexual dysfunction
- **Nerve:**, voice disorder, inability to speak and understand words, memory problem, unsteady gait, balance problems, one sided body weakness, sleepiness, nerve inflammation, distorted sense of smell, brain dysfunction, fainting, loss of consciousness, stroke, seizures
- **Eye:** itchy and red eyes, allergic reactions in eyes, drooping upper eyelid
- **Ear:** vertigo, ear clogging, ear discomfort
- **Heart:** irregular or fast heart beat, chest pain, accumulation of excess fluid around the heart, heart attack, heart failure
- **Blood vessels:** inflammation of a vein, hot flush
- **Lung and nasal passages:** runny nose, voice disorder, nasal clogging, pharyngeal erythema, hay fever
- **Gut and mouth:** fluid in the abdomen, gastroesophageal reflux disease, increased salivary secretion, excessive burping and belching, lip inflammation, gastrointestinal disorder, oral pain, abnormal contractions of muscles of the oesophagus, blockage in the stomach and intestine, stomach ulcer, retroperitoneal fibrosis, teeth that crack or break easily, swallowing difficulty, disorder of the salivary gland, haemorrhoids
- **Skin:** loss of skin colour, peeling skin, excessive body hair, nail shrinkage, excessive sweating,
- **General:** general condition worsening, weight increase, redness and swelling at the injection site, cancer pain and bleeding, multiple organ failure
- **Changes in blood tests:** high blood sugar, high blood lipids, changes in blood clotting time, high blood cell counts, low or high protein level
- **Other:** frequent urination, blood in urine, neck pain, back pain, breast pain, muscle tightness or cramps, joint swelling, limb discomfort, muscle weakness, arthritis inflammation and pain

Rare side effects (affect 1 to 10 users in 10,000) and very rare side effects (affect less than 1 user in 10,000) include:

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- pancreas infection
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If you experience any of the side effects or if you notice any side effects not listed in this leaflet, please tell your doctor.

If any of the side effects get serious, stop taking Teysuno and tell your doctor immediately.

5. HOW TO STORE TEYSUNO

- Keep out of the reach and sight of children.
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6. FURTHER INFORMATION

What Teysuno contains

- The active substances are tegafur, gimeracil and oteracil. Each hard capsule contains 20 mg tegafur, 5.8 mg gimeracil, and 19.6 mg oteracil monopotassium corresponding to 15.8 mg oteracil.
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Capsule contents: lactose monohydrate, magnesium stearate
Capsule shells: gelatin, titanium dioxide (E171), sodium lauryl sulphate, talc
Ink: red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminium lake (E132), carnauba wax, bleached shellac, glyceryl monooleate

What Teysuno looks like and contents of the pack

The hard capsules have a white body and white cap imprinted "TC442" in grey.

Each pack contains either 42 capsules (3 blisters of 14 capsules each) or 84 capsules (6 blisters of 14 capsules each)

Marketing Authorisation Holder

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Manufacturer

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