To be sold by retail only under prescription of medical specialists

TEGOYES

1. Generic Name

Tegafur, Gimeracil and Oteracil Capsules

2. Qualitative and quantitative Composition:

TEGOYES 15

Each hard gelatin capsule contains:

Tegafur J.P. …….15 mg

Gimeracil …….4.35 mg

Oteracil Potassium Eq. to Oteracil ……..11.8 mg

Excipients ……q. s.

Approved colours used in capsule shell

The excipients used are Lactose Monohydrate, Magnesium Stearate and Empty hard gelatin capsules.

TEGOYES 20

Each hard gelatin capsule contains:

Tegafur J.P. ……..20 mg

Gimeracil …….5.8 mg

Oteracil Potassium Eq. to Oteracil ……..15.8 mg

Excipients ……q. s.

Approved colours used in capsule shell

The excipients used are Lactose Monohydrate, Magnesium Stearate and Empty hard gelatin capsules.

3. Dosage form and strength

Dosage form: Capsules

Strength: Tegafur **15mg/20mg, Gimercil – 4.35mg/5.8mg, Oteracil – 11.8mg/15.8mg**

4. Clinical particulars

4.1 Therapeutic indication

It is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

4.2 Posology and method of administration

Posology

The TEGOYES must be taken as directed by the physician.

The recommended standard dose of Tegoyes when administered in combination with cisplatin is 25 mg/m^2 (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 Tegoyes and cisplatin doses and calculations according to body surface area (BSA) for doses of Tegoyes given in combination with cisplatin are provided in Table 1 and Table 2, respectively. The patient's BSA must be recalculated and the Tegoyes dose adjusted accordingly if a patient's weight increases or decreases by ≥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/m^2 by intravenous infusion administered once every 4 weeks. Cisplatin should be discontinued after 6 cycles without withdrawal of Tegoyes. If cisplatin is discontinued before 6 cycles, Tegoyes treatment alone can be resumed when the criteria for restarting it are met.

Patients treated with Tegoyes 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.

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

TEGOYES DOSES:

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

Medicinal product	**Standard dose (mg/m^2)**		**Dose reduction 1 (mg/m^2)**		**Dose reduction 2 (mg/m^2)**
Tegoyes	25[a]	→	20[a]	→	15[a]
and/or					
Cisplatin	75	→	60	→	45
[a] Expressed as Tegafur content.					

Tegoyes dose calculations

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

Tegoyes dose	**Each dose in mg (each dosing)[a]**	**Total daily dose in mg[a]**	**Number of capsules for each dose (2 doses/day)**	
Standard dose[a]: 25 mg/m^2			**15 mg capsulea (brown/white)**	**20 mg capsulea (white)**
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 m2	30	60	2	0
First dose reductiona: to 20 mg/m^2				
BSA ≥ 2.13 m2	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/m^2				
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 m2	15	30	1	0
Calculate BSA to 2 decimal places. [a] Expressed as tegafur content.				

<u>Adjustments during treatment</u>

General

Toxicity due to Tegoyes administration should be managed with symptomatic treatment and/or treatment interruption or dose reduction. Patients taking Tegoyes 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 Tegoyes dose has been reduced, it should not be increased again.

Tegoyes 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 Tegoyes capsules to be administered for each dose level. For minimum criteria for resumption of Tegoyes treatment.

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

During a 4-week cycle of treatment

Tegoyes 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 medicinal product 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 Tegoyes 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 Tegoyes for adverse reactions in general except for haematologic and renal toxicities.

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

Toxicity grades[a]	**Tegoyes dose changes within a 21-day treatment cycle**	**Tegoyes 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 Tegoyes. [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: Tegoyes and cisplatin dose modification according to creatinine clearance values at the start of a cycle of treatment

Creatinine clearance	**Tegoyes 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/mina	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
[a] Treatment for patients with CrCl <30 ml/min is not recommended unless the benefits of Tegoyes treatment clearly outweigh the risks. Refer to *"Dose modifications for special populations / Renal impairment* for guidance."		

Dose modifications for haematologic toxicities

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

Units	**Neutrophils**	**Platelets**	**Haemoglobin**	**Tegoyes dose modification**
IU	<0.5 x 109/l	<25 x 109/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 Tegoyes treatment

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

Non-haematologic	**Haematologic**
Baseline or Grade 1	Platelet count ≥100 x 109/l
Calculated creatinine clearance ≥30 ml/mina	Neutrophils ≥1.5 x 109/l
Haemoglobin ≥6.2 mmol/l	
CrCl must be calculated at the beginning of every cycle before the start of treatment with Tegoyes on Day 1.	
[a] Treatment for patients with CrCl <30 ml/min is not recommended unless the benefits of Tegoyes treatment clearly outweigh the risks. Refer to *"Dose modifications for special populations / Renal impairment for guidance."*	

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.
- 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.
- Severe renal impairment (CrCl below 30 ml/min)
  Although roughly similar daily exposure to 5-FU would be expected in patients with severe renal impairment at a dose of 20 mg/m2 once daily compared to 30 mg/m2 twice daily in patients with normal renal function, administration of Tegoyes is not recommended due to possibly higher incidence of adverse events of the blood and lymphatic system disorders unless the benefits clearly outweigh the risks.

- No data is available regarding Tegoyes administration in patients with end stage renal disease requiring dialysis.

Elderly

No adjustment of the standard dose is recommended in patients >70 years old

Hepatic impairment

No adjustment of the standard dose is recommended for patients with hepatic impairment.

Ethnicity

No adjustment of the standard dose is recommended for patients of Asian ethnicity.

Paediatric population

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

Method of administration

The capsules should be taken by mouth with water at least 1 hour before or 1 hour after a meal.

4.3 Contraindications

- hypersensitivity to the active substance (Tegafur, gimeracil, and oteracil) or to any of the excipients of this medication
- History of severe and unexpected reactions to fluoropyrimidine therapy.with myopathy
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- Pregnancy and breast-feeding
- Severe bone marrow suppression (severe leukopaenia, neutropaenia, or thrombocytopaenia.
- End stage renal disease patients requiring dialysis.
- Co-administration of other fluoropyrimidines with Tegoyes.
- Recent or concomitant treatment with brivudine (see section 4.4 and 4.5 for drug-drug interaction).
- Contraindications for cisplatin.

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 Tegoyes 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.

Hepatitis B reactivation

Administration of Tegoyes in hepatitis B virus carriers, HBc antigen negative and HBc antibody positive patients, or HBs antigen negative and HBs antibody positive patients may result in reactivation of hepatitis B.

Patients should be tested for HBV infection before initiating treatment with Tegoyes. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with Tegoyes should be closely monitored for signs and symptoms of active HBV infection throughout therapy, and follow-up monitoring for hepatic function tests or viral markers are recommended

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.

Renal toxicity

Treatment with Tegoyes 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 Tegoyes in combination with cisplatin. 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, Tegoyes and/or cisplatin dose should be adjusted according to Table 4, and appropriate supportive measures taken.

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.

Severe renal impairment

Treatment with Tegoyes is not recommended in patients with severe renal impairment due to possibly higher incidence of adverse events of the blood and lymphatic system and the possibility of unexpectedly higher exposure to 5-FU as a result of fluctuations in renal function in these patients, unless the benefits clearly outweigh the risks.

Ocular toxicity

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

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.

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 Tegoyes therapy.

Brivudine

Brivudine must not be administered concomitantly with Tegoyes. Fatal cases have been reported following capecitabine interaction. There must be at least a 4-week waiting period between end of treatment with brivudine and start of Tegoyes therapy. Treatment with brivudine can be started 24 hours after the last dose of Tegoyes (see section 4.3 and 4.5).
In the event of accidental administration of brivudine to patients being treated with Tegoyes, effective measures should be taken to reduce the toxicity of Tegoyes. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

DPD inducers

If a DPD inducer were to be concomitantly administered with Tegoyes, 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 Tegoyes cannot be evaluated.

Dihydropyrimidine dehydrogenase (DPD) deficiency:

DPD activity is rate limiting in the catabolism of 5-fluorouracil (see Section 5.2). Patients with DPD deficiency are therefore at increased risk of fluoropyrimidines-related toxicity including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity.
DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase.

Complete DPD deficiency

Complete DPD deficiency is rare (0.01-0.5% of Caucasians). Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with Tegoyes.

Partial DPD deficiency

Partial DPD deficiency is estimated to affect 3-9% of the Caucasian population. Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction.

Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Testing for DPD deficiency

Phenotype and/or genotype testing prior to the initiation of treatment with Tegoyes is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines.

Genotypic characterisation of DPD deficiency

Pre-treatment testing for rare mutations of the DPYD gene can identify patients with DPD deficiency.

The four DPYD variants c.1905+1G>A [also known as DPYD*2A], c.1679T>G [DPYD*13], c.2846A>T and c.1236G>A/HapB3 can cause complete absence or reduction of DPD enzymatic activity. Other rare variants may also be associated with an increased risk of severe or life-threatening toxicity.

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

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

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

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

Phenotypic characterisation of DPD deficiency

For phenotypic characterisation of DPD deficiency the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil (U) in plasma is recommended.

Elevated pre-treatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainties on uracil thresholds defining complete and partial DPD deficiency, a blood uracil level $\geq$ 16 ng/ml and < 150 ng/ml should be considered indicative of partial DPD deficiency and associated with an increased risk for fluoropyrimidine toxicity. A blood uracil level $\geq$ 150 ng/ml should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity.

Microsatellite instability (MSI)

Tegoyes 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 Tegoyes and MSI in gastric cancer is unknown.

Glucose/galactose intolerance/malabsorption

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

Other oral fluorpyrimidines

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

4.5 Drugs interactions

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

Brivudine

A clinically significant interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-Fluorouracil, Tegafur), resulting from the inhibition of dihydropyrimidine dehydrogenase by brivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, brivudine must not be administered concomitantly with Tegoyes. There must be at least a 4-week waiting period between end of treatment with brivudine and start of Tegoyes therapy. Treatment with brivudine can be started 24 hours after the last dose of Tegoyes.

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 Tegoyes and other fluoropyrimidines. The washout period described in the SmPC of other fluoropyrimidine medicinal products should be followed if Tegoyes is to be administered subsequent to other fluoropyrimidine medicinal products.

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 Tegoyes should be avoided as effectiveness of Tegoyes could be decreased.

Folinate/folinic acid

No data are available on the concomitant use of folinic acid with Tegoyes 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 nitromidazoles with Tegoyes in combination with cisplatin. However, nitromidazoles 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 Tegoyes.

Methotrexate

No data are available on the concomitant use of methotrexate with Tegoyes 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 Tegoyes.

Clozapine

No data are available on the concomitant use of clozapine with Tegoyes 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 Tegoyes.

Cimetidine

No data are available on the concomitant use of cimetidine with Tegoyes 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 Tegoyes.

Coumarin-derivative anticoagulant

The activity of a coumarin-derivative anticoagulant was enhanced by Tegoyes. Caution is advised as co-administration of Tegoyes and coumarin anticoagulation therapy may increase the risk of bleeding.

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 Tegoyes 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 Tegoyes should be avoided.

Food

Administration of Tegoyes with a meal reduced exposure to oteracil and gimeracil, with a more pronounced effect for oteracil than for gimeracil. It should be taken with water at least 1 hour before or 1 hour after a meal.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Women of childbearing potential/Contraception in males and females

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

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

Pregnancy

Tegoyes is contraindicated in pregnancy. There have been some case reports of foetal abnormalities. Studies in animals have shown reproductive toxicity. As with other fluoropyrimidines, Tegoyes administration caused embryolethality and teratogenicity in animals . If the patient becomes pregnant while receiving Tegoyes, treatment should be discontinued and the potential risk to the foetus must be explained. Genetic counseling should be considered.

Breast-feeding

Tegoyes is contraindicated during breast-feeding. It is not known whether Tegoyes or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of Tegoyes or its metabolites in milk.

A risk to newborns/infants cannot be excluded. Breast-feeding must be discontinued while receiving treatment with Tegoyes..

Fertility

No reported data are available on the effect of Tegoyes in combination with cisplatin on human fertility. Non-clinical studies demonstrated that Tegoyes did not appear to affect male or female fertility in the rat.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

The overall safety profile of Tegoyes 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 Tegoyes 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

Tabulated list of adverse reactions

The following headings are used to rank the adverse reactions by frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 Tegoyes 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 Tegoyes-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 Classa	**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	Hepatitis B reactivation
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)			Tumour haemorrhage, cancer pain	

Blood and lymphatic system disorders	Neutropenia, leukopenia, anaemia, thrombo-cytopenia	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, hypophosphatameia, 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	Leukoenceph-alopathy, anosmia
Eye disorders		Vision disorder, lacrimal disorder, conjunctivitis, corneal disorder [b]	Eye allergy, eyelid ptosis, erythema of eyelid	

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 brittl	Acute pancreatitis
Hepatobiliary disorders		Hyperbilirubin-aemia, alanine aminotransferase increased, aspartate	Liver function test abnormal, gamma glutamyltransferase increased	Acute hepatic failure

		aminotransferase increased		
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia 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	
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	
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.
[a]incl corneal epithelium defect, corneal erosion, corneal lesion, corneal opacity, corneal perforation, keratitis, punctate keratitis, ulcerative keratitis, limbal stem cell deficiency, visual acuity reduced, visual impairment, vision blurred.

Other clinical studies with Tegoyes in combination with cisplatin

Although studies of Tegoyes 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.

Post-marketing surveillance experience in gastric cancer patients

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

Comparison of safety between 71 patients ≥70 years old (elderly) and 450 patients <70 years old treated with Tegoyes 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 Tegoyes 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.

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

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 Tegoyes 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, the most common adverse reactions reported over all cycles across all cohorts were diarrhoea (57.6%), nausea (42.4%), vomiting (36.4%), fatigue (33.3%) and anaemia (24.2%). In this study, 7 patients with moderate renal impairment were treated with 20 mg/m2 Tegoyes twice daily, while 7 patients with severe renal impairment received Tegoyes 20 mg/m2 once daily. No dose limiting toxicities were observed in Cycle 1 in patients with moderate or severe renal impairment. The incidence of blood and lymphatic systems disorders adverse reactions observed across all cycles in the moderate and severe renal impairment patients were 28.6% and 44.4%, respectively. The dose for one patient in the severe cohort was reduced to 13.2 mg/m2 once daily at the start of Cycle 12 due to an adverse reaction (Grade 2 diarrhoea) in Cycle 11.

Paediatric population

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

Reporting of suspected adverse reactions

Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting
By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

The highest single dose of Tegoyes 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 Mechanism of Action

Tegoyes 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.

5.2 Pharmacodynamic properties

In a dose escalation study comparing the tolerability of 5-FU in Tegoyes 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 (Cmax) and area under the concentration-time curve (AUC) values were approximately 3-fold higher after Tegoyes administration than after administration of Tegafur alone, despite a 16-fold lower Tegoyes 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 Tegoyes 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 Tegoyes components.

Clinical efficacy and safety

A reported Phase I study established the current regimen by evaluating cohorts of Tegoyes 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 reported Phase III FLAGS study, there was no apparent relationship between 5-FU AUC (Tegoyes/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).

In the reported Phase III FLAGS study, there was no apparent relationship between 5-FU AUC (Tegoyes/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).

A reported Phase I study was conducted to evaluate the PK of the components of Tegoyes and their metabolites in cancer patients with impaired renal function compared to those with normal renal function. In this study, antitumor activity was measured by best overall tumour response. The majority (70.4%) of patients had Stable Disease as a best response (based on Investigator's assessment using RECIST criteria) and 29.6% patients had Progressive Disease as their best overall response. No dose limiting toxicities were observed in the first cycle of treatment.

Advanced gastric cancer

Data from a multicentre, multinational (excluding Asia), randomised, controlled, open-label Phase III clinical study (FLAGS) support the use of Tegoyes in combination with cisplatin for the treatment of patients with advanced gastric cancer. In this study, 521 patients were randomised to treatment with Tegoyes (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).

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

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

For the primary endpoint of overall survival, Tegoyes in combination with cisplatin was non-inferior to 5-FU in combination with cisplatin. 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

	Tegoyes + Cisplatin		5-FU + Cisplatin		
Endpoint Population	**N**	**Median [95% CI]. months**	**N**	**Median [95% CI], months**	**Hazard Ratio [95% CI]**
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 Tegoyes in all subsets of the paediatric population in gastric adenocarcinoma.

5.3 Pharmacokinetic properties

The single and multiple dose pharmacokinetics (PK) of Tegoyes 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 Tegoyes (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 Tmax for Tegoyes components Tegafur, gimeracil, and oteracil was 0.5, 1.0, and 2.0 hours, respectively, and the mean ± standard deviation (SD) AUC0-inf and Cmax 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 Tmax for 5-FU was 2.0 hours and the mean AUC0-inf and Cmax 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 Tmax of Tegafur, gimeracil, and oteracil was 0.8, 1.0, and 2.0 hours, respectively, and the corresponding mean ± SD AUC(0-12h) and Cmax 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 Tmax for 5-FU was 2.0 hours and the mean AUC(0-12h) and Cmax was 870 ± 405 ng.hr/ml and 165 ± 62 ng/ml, respectively.

Administration of Tegoyes under fed conditions resulted in decreased AUC0-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 AUC0-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 AUC0-inf and Cmax for 5-FU were approximately 3-fold greater following administration of Tegoyes (50 mg expressed as Tegafur content) than following administration of Tegafur alone

(800 mg), while AUC0-inf and Cmax values for the 5-FU metabolite α-fluoro-β-alanine (FBAL) were approximately 15- to 22-fold lower following administration of Tegoyes than following administration of Tegafur.

The oteracil component of Tegoyes 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 Tegoyes. Although no intravenous data are available for Tegoyes 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'-phosphosulfphate 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 Tegoyes (reflecting DPD inhibition by gimeracil). Following both single dose (50 mg) and multiple dose (30 mg/m2 twice daily) administration of Tegoyes 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 (T1/2) of 5-FU observed after administration of Tegoyes (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 Tegoyes, T1/2 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 Tegoyes, 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 Tegoyes dose (total Tegoyes + 5-FU + FBAL). There was no effect of gimeracil on renal clearance of tegafur, FBAL, and 5-FU following administration of Tegoyes as compared to their clearance following administration of tegafur alone..

Linearity/non-linearity

In a reported 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.

Special Populations

A population PK analysis of Tegoyes 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 Tegoyes pharmacokinetics observed with increasing age was related to change in renal function as measured by creatinine clearance.

Renal impairment

In a reported Phase I Tegoyes 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 AUC0-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 AUC0-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 Tegoyes 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.

Following a reduced dose of Tegoyes 20 mg/m2 administered once daily to the severe renal impairment group (CrCl < 30 ml/min), the single-dose AUC0-inf and multiple-dose AUC0-τ values for 5-FU were approximately 2-fold higher in the severe renal impairment group compared to those observed in the normal renal function group receiving 30 mg/m2 twice daily. Therefore, the daily exposure to 5-FU would be expected to be comparable in these groups, since the daily exposure in patients in the severe renal impairment group is based on the administration of Tegoyes once a day, while the daily exposure to 5-FU in the patients with normal renal function is based on the administration of Tegoyes twice daily. However, it is to be noted that the exposure to 5-FU can be variable and unexpectedly higher in patients with severe renal impairment due to the impact of fluctuations in renal function in these patients.

Hepatic impairment

There were no significant differences in AUCs of 5-FU, tegafur, gimeracil, or oteracil after either single or multiple dose administration of Tegoyes 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 Cmax 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 Tegoyes 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 T1/2 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 Tegoyes 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 Tegoyes 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 Tegoyes in paediatric patients.

6. Nonclinical properties

6.1 Animal toxicology or Pharmacology

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 Tegoyes 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.

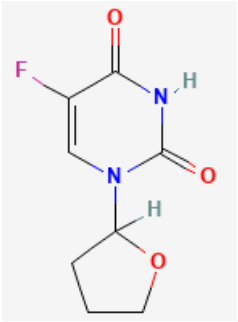
Tegoyes does not appear to affect male or female fertility in the rat; however, administration at any time after conception resulted in a range of external, visceral, and skeletal foetal abnormalities in rat and rabbit. There is therefore a high risk for developmental toxicity at clinical doses, primarily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

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

7. Description

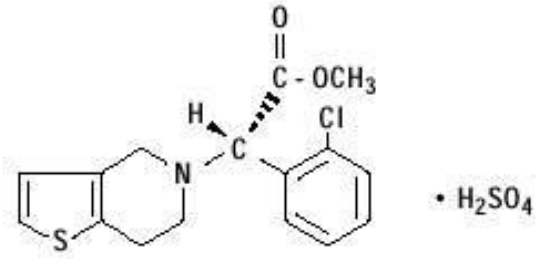
TEGAFUR

Tegafur is 5-fluoro-1-(oxolan-2-yl) pyrimidine-2,4-dione. The empirical formula is $C_8H_9FN_2O_3$ and its molecular weight is 200.17. Its structural formula is:



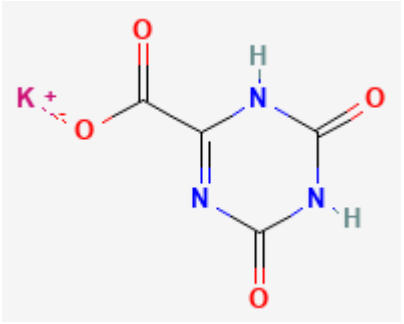
GIMERCIL

Gimeracil is 5-chloro-4-hydroxy-1H-pyridin-2-one. The empirical formula is $C_5H_4ClNO_2$ and its molecular weight is 145.54. Its structural formula is:



OTERACIL

Oteracil Potassium is potassium;4,6-dioxo-1H-1,3,5-triazine-2-carboxylate. The empirical formula is $C_4H_2KN_3O_4$ and its molecular weight is 195.17. Its structural formula is:



Tegafur, Gimeracil and Oteracil Capsules are white to off white powder filled in size '4' hard gelatin capsule. The excipients used are Lactose Monohydrate, Magnesium Stearate and Empty hard gelatin capsules.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

TEGOYES is available in Blister strip of 7 capsules

8.4 Storage and handing instructions

Store below 30°C. Protect from direct light & moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

TEGOYES

Tegafur, Gimeracil and Oteracil Capsules

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What is TEGOYES and what it is used for

Tegoyes contains the active substances tegafur gimeracil and oteracil.

Tegoyes belongs to the fluoropyrimidine class of medicines known as "antineoplastic agents" which stop the growth of cancer cells.

It is used in adults for the treatment of advanced gastric cancer when given in combination with cisplatin.

9.2 What you need to know before you take TEGOYES

Do not take TEGOYES

- are allergic to tegafur, gimeracil, oteracil or any of the other ingredients of this medicine.
- are taking other fluoropyrimidine anti-cancer medicine such as fluorouracil and capecitabine, or have had severe and unexpected reactions to fluoropyrimidines
- know that you do not have any activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (complete DPD deficiency)
- are pregnant or breast-feeding
- have severe blood disorders
- have kidney disease requiring dialysis
- are being treated now or have been treated in the last 4 weeks with brivudine as part of herpes zoster (chickenpox or shingles) therapy.

Warnings and precautions

Talk to your doctor or pharmacist before taking TEGOYES.

- 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
- a current or previous infection of the liver with the hepatitis B virus, since your doctor may want to monitor you more closely
- a partial deficiency in the activity of the enzyme dihydropyrimidine dehydrogenase (DPD)
- a family member who has partial or complete deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD).

DPD deficiency: DPD deficiency is a genetic condition that is not usually associated with health problems unless you receive certain medicines. If you have DPD deficiency and take Tegoyes, you are at an increased risk of severe side effects (listed under section 4 Possible side effects). It is recommended to test you for DPD deficiency before start of treatment. If you have no activity of the enzyme you should not take Tegoyes. If you have a reduced enzyme activity (partial deficiency) your doctor might prescribe a reduced dose. If you have negative test results for DPD deficiency, severe and life-threatening side effects may still occur.

Children and adolescents

Tegoyes is not recommended for children under 18 years of age.

Other medicines and TEGOYES

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You must not take brivudine (an anti-viral medicine for the treatment of shingles or chickenpox) at the same time as Tegoyes treatment (including during any rest periods when you are not taking any Tegoyes capsules).

If you have taken brivudine you must wait for at least 4 weeks after stopping brivudine before starting to take Tegoyes. See also section "Do not take Tegoyes".

Also, you need to be particularly careful if you are taking any of the following:

- other fluoropyrimidine based medicines such as the anti-fungal flucytosine. Tegoyes cannot be substituted for other oral fluoropyrimidine medicine.

- inhibitors of the enzyme CYP2A6 which activates Tegoyes such as tranylcypromine and methoxsalen

- folinic 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

Pregnancy, breast-feeding and fertility

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 Tegoyes if you are pregnant or think you might be.

During and up to 6 months after treatment with Tegoyes, 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 Tegoyes.

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

Driving and using machines

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

9.3 How to take TEGOYES

Always take Tegoyes 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 Tegoyes 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.

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

Tegoyes 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.

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

If you take more TEGOYES than you should:

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

If you forget to take TEGOYES

Do not take the missed dose at all and do not take a double dose to make up for a forgotten dose. Instead, continue your regular dosing schedule and check with your doctor.

If you stop taking TEGOYES

Do not stop the treatment unless your doctor tells you so. Contact your doctor or pharmacist before stopping.

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

9.4 Possible side effects

Like all medicines, Tegoyes 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.

Very common side effects (may affect more than 1 in 10 people) include:
o 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 Tegoyes 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 Tegoyes 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 38.5o C or higher, stop taking Tegoyes 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 Tegoyes 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 apetite (anorexia) can lead to weight loss and dehydration

o You may become dehydrated if you do not eat and/or drink enough water.

o If you become dehydrated you may have symptoms such as dry mouth, weakness, dry skin, dizziness, cramping

o 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.

o 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 (may affect 1 to 10 in 100 people) include:

- Nerve: headache, dizziness, sleeplessness, changes in taste

- Eye: eye problems, increased or decreased tearing discomfort, vision problems, serious illness with blistering of the eyes, wearing away of the surface "skin" of the eye (corneal erosion).

- 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 (may affect 1 to 10 in 1,000 people) 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 (may affect 1 to 10 in 10,000 people) and very rare side effects (may affect less than 1 in 10,000 people) include:

- acute liver failure

- pancreas infection

- muscle breakdown

- loss of sense of smell

- sun allergy

- widespread blood clotting and bleeding

- disease affecting the white matter of the brain

- serious illness with blistering of the skin, mouth and genitals

recurrence (reactivation) of hepatitis B infection when you have had hepatitis B in the past (a liver infection)

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting
By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store TEGOYES

Store below 30°C. Protect from direct light & moisture.

9.6 Contents of the pack and other information

The active substance in TEGOYES are Tegafur, Gimeracil and Oteracil Capsules available in strength of Tegafur - 15mg/20mg, Gimercil – 4.35mg/5.8mg, Oteracil – 11.8mg/15.8mg

TEGOYES 15

The excipients used are Lactose Monohydrate, Magnesium Stearate and Empty hard gelatin capsules.

TEGOYES is available in Blister strip of 7 capsules.

TEGOYES 20

The excipients used are Lactose Monohydrate, Magnesium Stearate and Empty hard gelatin capsules.

TEGOYES is available in Blister strip of 7 capsules.

10. Details of manufacturer

Manufactured in India by:

BDR Pharmaceuticals Int'l Pvt. Ltd.

R. S. No. 578, Near Effluent Channel Road,

Vill. Luna, Tal. Padra, Dist. Vadodara-391440.

11. Details of permission or license number with date

Mfg. Lic. No.: G/25/2071 issued on 04.03.2022.

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TEGOYES 15 and 20 mg/FEB 22/01/PI