CISplatin and Teysuno® - 28 day cycle

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of advanced gastric cancer when given in combination with CISplatin.	C16	00235a	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Teysuno® is administered twice daily, morning and evening, for 21 days followed by 7 days rest (**28-day treatment cycle**) until disease progression or unacceptable toxicity develops.
CISplatin is administered once every 4 weeks for 6 cycles until disease progression or unacceptable toxicity develops. If CISplatin is discontinued before 6 cycles in patients with responding disease, Teysuno® treatment alone can be resumed when the criteria for restarting it are met.

Facilities to treat anaphylaxis MUST be present when CISplatin is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1-21	Teysuno®	[a,b]25mg/m^2 twice daily	PO	Take with water at least 1 hour before or 1 hour after a meal.	Continuously (day 1-21 of each 28 day cycle)
1	[c]CISplatin	75mg/m^2	IV infusion	1000ml 0.9% sodium chloride over 60 minutes.	Every 28 days for up to 6 cycles
[a]Dose expressed in terms of tegafur content. **Teysuno® is available as a hard capsule containing 15mg tegafur, 4.35mg gimeracil and 11.8mg oteracil.**					
If a patient vomits after taking a dose, this dose should not be replaced.					
[b] See dose modifications section for patients with identified partial DPD deficiency					
[c]**Pre and post hydration therapy required for CISplatin** See local hospital policy recommendations. Suggested prehydration for CISplatin therapy: 1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes. Administer CISplatin as described above Post hydration: Administer 1000 ml 0.9% NaCl over 60mins					
Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.					

ELIGIBILITY:

- Indications as above
- ECOG status 0-1.
- Adequate haematological, renal and liver status.

EXCLUSIONS:

Teysuno®

- Hypersensitivity to tegafur, gimeracil, oteracil or any of the excipients.
- History of severe and unexpected reactions to fluoropyrimidine therapy.
- Known complete DPD deficiency
- Pregnancy and breastfeeding.
- Severe bone marrow depression.
- End stage renal disease patients requiring dialysis.
- Co-administration of other fluoropyrimidines with Teysuno®.
- Treatment within 4 weeks with DPD enzyme inhibitors, including sorivudine or its chemically related analogues such as brivudine.

CISplatin

- Hypersensitivity to CISplatin or other platinum containing compounds.
- Renal impairment.
- Pre-existing hearing impairment.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DPD testing prior to first treatment with tegafur using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile weekly.
- Evaluate for peripheral neuropathy and ototoxicity prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Consider a reduced starting dose in patients with identified partial DPD deficiency.
    - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

- 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 ≥10% from the one used for the previous calculation of BSA and the change is clearly not related to fluid retention.
- Toxicity due to Teysuno® administration should be managed with symptomatic treatment and/or treatment interruption or dose reduction.
- Doses omitted for toxicity are not replaced.
- Once the dose of Teysuno® has been reduced it should not be increased again.
- Dose modifications for toxicity can be made according to Table 1.

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

	Standard dose	Dose Reduction 1	Dose Reduction 2
Teysuno®	***25 mg/m²**	***20 mg/m²**	***15 mg/m²**
and/or			
CISplatin	**75mg/m²**	**60 mg/m²**	**45 mg/m²**
***Dose expressed in terms of tegafur content.**			

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

	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)
BSA ≥ 2.30m²	60	120	0	3
BSA = 2.10-2.29m²	55	110	1	2
BSA = 1.90-2.09m²	50	100	2	1
BSA = 1.70-1.89m²	45	90	3	0
BSA = 1.50-1.69m²	40	80	0	2
BSA = 1.30-1.49m²	35	70	1	1
BSA ≤ 1.29m²	30	60	2	0
First dose reduction[a]: to 20mg/ m²				
BSA ≥ 2.13m²	45	90	3	0
BSA = 1.88-2.12m²	40	80	0	2
BSA = 1.63-1.87m²	35	70	1	1
BSA = 1.30-1.62m²	30	60	2	0
BSA ≤ 1.29m²	20	40	0	1
Second dose reduction[a]: to 15mg/ m²				
BSA ≥ 2.17m²	35	70	1	1
BSA = 1.67-2.16m²	30	60	2	0
BSA = 1.30-1.66m²	20	40	0	1
BSA ≤ 1.29m²	15	30	1	0
Calculate BSA to 2 decimal places. [a]Expressed as tegafur content				

Dose modification during a 4 week cycle of treatment:

- 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.

Dose modification at the initiation of subsequent cycles of treatment:

- If treatment delay is indicated for either Teysuno® or CISplatin then administration of both medicinal products should be delayed until the requirements for starting both are met unless one of the products has been permanently discontinued.

Haematological:

Table 3: Dose modification of for haematological toxicity

ANC ($x10^9$/L)	Haemoglobin (mmol/L)	Platelets ($x10^9$/L)	Teysuno Dose modification
< 0.5	4	< 25	Suspend treatment until levels below are reached
On recovery to			
≥ 1.5	≥ 6.2	≥ 100	Treatment may be resumed at one reduced dose level

Renal and Hepatic Impairment:

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

Table 4: Dose modifications based on renal function

Creatinine Clearance	Teysuno® dose modification	CISplatin dose modification
≥ 50ml/min	No dose modification	No dose modification
30 to 49 ml/min	Start treatment at one reduced dose level	50% dose reduction from previous cycle
< 30ml/min	Suspend treatment until resumption criterion (≥30ml/min) is met and then start treatment at one reduced dose level.	Suspend CISplatin treatment until resumption criterion (≥30ml/min) is met and then start treatment at a 50% dose reduction from the previous cycle
Treatment for patients with CrCl < 30ml/min is not recommended unless the benefits of Teysuno® treatment clearly outweigh the risks.		

Table 5: Dose modifications for hepatic impairment

Drug	Hepatic Impairment
Teysuno	No adjustment of the standard dose is recommended
CISplatin	No dose reduction necessary

Management of adverse events:

Table 6: Teysuno® dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Grade 2 [a,b]	Suspend treatment with Teysuno® until grade 1. Treatment may then be resumed at previous dose level.
Grade 3 or higher [b] First occurrence	Suspend treatment with Teysuno® until grade 1. Resume treatment at 1 dose level less than previous level.
Second occurrence	Suspend treatment with Teysuno® until grade 1. Resume treatment at 1 dose level less than previous level.
Third occurrence	Discontinue
[a]For Grade 2 nausea and/or vomiting, the anti-emetic therapy should be optimized prior to a suspension of Teysuno®. [b]Patient may continue with treatment without reduction or interruption for adverse reactions (irrespective of grade) considered unlikely to become serious or life threatening at the discretion of the prescribing consultant.	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CISplatin - High**. (Refer to local policy).**

Teysuno® - Low. If used as single agent low emetogenicity and no need for antiemetics or hydration.

PREMEDICATIONS:

Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above).**

OTHER SUPPORTIVE CARE:

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.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Bone marrow suppression:** Treatment-related bone marrow suppression, including neutropenia, leucopoenia, thrombocytopenia, anaemia, and pancytopenia, 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 neutropenia and treated as medically indicated (e.g., with antibiotics, granulocyte-colony stimulating factor [G-CSF])
- **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. 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. 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 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). 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 3, and appropriate supportive measures taken
- **Ocular toxicity** The most common treatment-related ocular disorders among patients in studies in Europe/USA treated with Teysuno® in combination with CISplatin were lacrimal disorders, 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.
- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of CISplatin to such patients is contraindicated.
- **Nephrotoxicity**: Renal toxicity is common with CISplatin. Encourage oral hydration.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. infusions.
- **Extravasation:** CISplatin causes irritation if extravasated **(Refer to local policy).**
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- 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.
- Teysuno® must not be used with sorivudine or brivudine or within 4 weeks of the last dose of sorivudine or brivudine or any other DPD enzyme inhibitor.

- Close monitoring of INR and PT required in patients receiving coumarin-derived anticoagulants and Teysuno® therapy for increased bleeding tendency.
- Avoid concurrent use of CISplatin and nephrotoxic and ototoxic drugs (e.g. loop diuretics and aminoglycosides).
- CISplatin may reduce serum phenytoin levels.
- Current drug interaction databases should be consulted for more information

ATC CODE:

Tegafur, combinations	L01BC53
CISplatin	L01XA01

REFERENCES:

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3. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Aug 2020 Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v-)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0
4. Teysuno® Summary of Product Characteristics Accessed Oct 2020 Available at: https://www.ema.europa.eu/en/documents/product-information/teysuno-epar-product-information_en.pdf
5. Cisplatin 1mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics. Accessed Oct 2020 Available athttps://www.hpra.ie/img/uploaded/swedocuments/Final%20approved%20SPC%20PA0822.199.001.pdf

Version	Date	Amendment	Approved By
1	1/11/2014		Dr Gregory Leonard, Dr Maccon Keane
2	21/10/2016	Removed statement re additional monitoring	Dr Maccon Keane

3	26/09/2018	Updated with new NCCP regimen template. Updated hydration protocol for CISplatin	Dr Maccon Keane
4	10/11/2020	Reviewed. Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020. Updated adverse effects section regarding Hep B reactivation as per spc.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.