DPD: tegafur with DPD inhibitor 2553/2554/4891/4892

AS = gene activity score, AS 0 = gene activity score 0 = two non-functional alleles (*2A/*2A, *2A/*13 or *13/*13) or more general two gene variants leading to non-functional alleles (*2A-homozygosity, *13-homozygosity, or both *2A and *13), AS 1 = gene activity score 1 = one fully functional and one non-functional allele (*1/*2A or *1/*13), AS 1.5 = gene activity score 1.5 = one fully functional and one partially functional allele (*1/1236A or *1/2846T), AS 2 = gene activity score 2 = two fully functional alleles (normal metaboliser; *1/*1), DPD = dihydropyrimidine dehydrogenase, FENO = fenotyping = two partially functional alleles (1236A/1236A, 1236A/2846T or 2846T/2846T) or one non-functional and one partially functional allele (*2A/1236A, *2A/2846T *13/1236A or *13/2846T) or more general two gene variants leading to partially functional alleles (1236A-homozygosity, 2486T-homozygosity, or both 1236A and 2846T) or a gene variant leading to a non-functional allele and a gene variant leading to a partially functional allele (*2A plus 1236A, *2A plus 2846T, *13 plus 1236A or *13 plus 2846T), NS = non-significant, S = significant, SmPC = Summary of Product Characteristics.

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

Brief summary and justification of choices:
Tegafur is converted in the body to fluorouracil. DPD converts fluorouracil to inactive metabolites. The enzyme therefore reduces the percentage of fluorouracil that is converted to the active metabolite. This is also the case when tegafur is combined with a DPD inhibitor, because inhibition by DPD inhibitors is reversible and reduces over time.
Genetic variations in DPD lead to reduced enzyme activity, which results in an increased percentage of tegafur that is converted to the active metabolite. Therapeutic and toxic concentrations of the active metabolite are therefore reached at lower doses. If the dose is left unchanged, the risk of severe toxicity is increased for gene activity scores 1-1.5 and especially so for gene activity score 0 and fenotyping.
This is why it was decided that this concerns a gene-drug interaction and that therapy adjustment is required, either choosing an alternative or reducing the dose (yes/yes-interactions).
You can find an overview of the clinical and kinetic effects per phenotype group in the background information text of the gene-drug interactions on the KNMP Kennisbank. You may also have access to this background text via your pharmacy or physician information system. Substantiation for the recommendation for each phenotype group is provided below.
Justification of the recommendation for each phenotype group

AS 0: There are no data on the use of tegafur in combination with a DPD inhibitor for gene activity score 0. The SmPCs state that tegafur in combination with a DPD inhibitor is contraindicated in patients with dihydropyrimidine dehydrogenase deficiency, but do not substantiate this.
However, two patients using standard doses of tegafur-uracil who developed severe toxicity were found for each of the partially deficient phenotypes gene activity score 1 and 1.5. The toxicity was similar to that found in patients treated with capecitabine or fluorouracil, both of which are given without a DPD inhibitor.
The DPD inhibitor is 200x more potent in the tegafur-gimeracil-oteracil combination. However, fluorouracil is still metabolised by DPD after administration of this combination and DPD is therefore also involved in fluorouracil clearance.
For fluorouracil and capecitabine, the maximally tolerated dose of 50% of the normal dose for *1/*2A indicates that the maximally tolerated dose for *2A/*2A (gene activity 0) is close to zero, as do the scarce data on tolerated doses in patients with gene activity 0. For this reason, an alternative is advised.
There is a fairly good correlation between the residual DPD enzyme activity in peripheral blood mononuclear cells and the tolerated fluorouracil or capecitabine dose. Therefore, if an alternative is not possible, adjusting the dose according to the residual DPD enzyme activity in peripheral blood mononuclear cells is advised. This strategy has been shown to be feasible for capecitabine in two patients with genotype *2A/*2A. A patient with 0.5% of the normal DPD activity tolerated 0.8% of the normal capecitabine dose (150 mg every 5 days). A patient with undetectable DPD activity, tolerated 0.43% of the normal capecitabine dose (150 mg every 5 days with every third dose skipped).This is why this strategy is also recommended for tegafur in case an alternative is not possible.

FENO: There are no data on the use of tegafur in combination with a DPD inhibitor for 'fenotyping'. The SmPCs state that tegafur in combination with a DPD inhibitor is contraindicated in patients with a history of serious and unexpected reactions to fluoropyrimidine therapy, but do not substantiate this.
However, two patients using standard doses of tegafur-uracil who developed severe toxicity were found for each of the partially deficient phenotypes gene activity score 1 and 1.5. The toxicity was similar to that found in patients treated with capecitabine or fluorouracil, both of which are given without a DPD inhibitor. The recommendation for fluorouracil and capecitabine in patients in the genotype group fenotyping is to fully personalise therapy in these patients, i.e. measure DPD enzyme activity and adjust the fluoropyrimidine dose accordingly or to choose an alternative. This is why full personalisation of therapy or an alternative is also recommended for tegafur.

AS 1: Treatment with tegafur in combination with the DPD inhibitor uracil in two patients with gene activity score 1 led to similar toxicity as found after treatment with fluorouracil or capecitabine. However, four patients with gene activity score 1 could be treated with 90% of the standard tegafur-uracil dose without grade 3-4 toxicity occurring. Similar to data found for fluorouracil and capecitabine, treatment with a reduced dose of tegafur-uracil seems possible for patients with gene activity score 1. This is why a dose reduction or alternative is recommended.

AS 1.5: Treatment with tegafur in combination with the DPD inhibitor uracil in two patients with gene activity score 1.5 (one with genotype *1/1236A and one with genotype *1/2846T) led to similar toxicity as found after treatment with fluorouracil or capecitabine. However, four patients with the more deficient phenotype gene activity score 1 could be treated with 90% of the standard tegafur-uracil dose without grade 3-4 toxicity occurring. Similar to data found for fluorouracil and capecitabine, treatment with a reduced dose of tegafur-uracil seems possible for patients with gene activity score 1 or higher. This is why a dose reduction or alternative is recommended.

Recommendation concerning pre-emptive genotyping, including justification of choices:

The Dutch Pharmacogenetics Working Group considers genotyping before starting tegafur with DPD inhibitors to be essential for drug safety. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection.

The clinical implication of the gene-drug interaction scores 2 out of the maximum of 10 points based on only the data on tegafur with DPD inhibitor, but 8 out of the maximum of 10 points when also the analogy with systemic fluorouracil and capecitabine is taken into account. Because of the comparable severity of toxicity on tegafur with DPD inhibitor and on fluorouracil/capecitabine found for 3 patients in a case report and the use of both tegafur with DPD inhibitor and capecitabine being contra-indicated in patients with DPD deficiency in the drug labels, the Dutch Pharmacogenetics Working Group considers it justified to take into account the analogy with systemic fluorouracil and capecitabine and use the clinical implication score of 8 points (with pre-emptive genotyping being essential for scores ranging from 6 to 10 points). The scores on each of the four criteria of the clinical implication score are indicated below.

Serious life-threatening toxicity on full dose tegafur with DPD inhibitor was shown in 4 patients (gene activity scores either 1 or 1.5). The severity of the toxicity was comparable with the severity, that 3 of these patients experienced earlier on fluorouracil or capecitabine. Extrapolation to patients with gene activity score 0, suggests that the toxicity on tegafur with DPD inhibitor can be fatal (grade 5). This results in the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (2 points for CTCAE grade 5).

The increased risk for serious toxicity (code E corresponding to grade 4) has only been shown in one case series for tegafur, while another series of 4 cases who developed grade 4 toxicity on fluorouracil or capecitabine did not develop grade ≥ 3 toxicity on 90-100% of the normal dose of tegafur with DPD inhibitor. However, the case series showing serious toxicity is supported by the fact that the DPD inhibitor is cleared faster than tegafur. In addition, the drug label warns that irreversible inhibition of DPD can lead to increased clinically significant fluoropyrimidine-related toxicities with potentially fatal outcomes. The diminished DPD activity resulting from gene variants is irreversible. Therefore, it is rational to extrapolate the supporting evidence of 18 studies and 3 meta-analyses with an increased risk for serious life-threatening toxicity (code E corresponding to grade 4) for fluorouracil and capecitabine to tegafur with DPD inhibitor. This results in the maximum score of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for three or more publications with level of evidence score ≥ 3).

The number needed to genotype cannot be deduced from the literature for tegafur with DPD inhibitor, but was deduced from two articles on a large Dutch study with fluorouracil and capecitabine to be 163. The calculated number to genotype of 163 results in 1 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 (1 point for 100 ≤ NNG ≤ 1000).

The Summary of Product Characteristics (SmPC) indicates that tegafur with DPD inhibitor is contra-indicated both in patients with known DPD deficiency (gene activity score 0) and in patients with a history of severe and unexpected reactions to fluoropyrimidine therapy (for which the risk is increased in patients with gene activity score 1-1.5 and 'fenotyping'). This results in the maximum number of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (2 points for at least one genotype/phenotype mentioned as a contra-indication in the corresponding section).

In addition to the clinical implication score indicating pre-emptive genotyping to be essential, for fluorouracil and capecitabine, three cost analyses suggest that the costs for genotyping of all patients are less than the costs of treating the additional patients with toxicity if genotyping is not performed. Thus, pre-emptive genotyping might not only be essential, but also cost-saving.

The table below follows the KNMP nomenclature for the gene variants. The nomenclature for the gene variants used in the table below may therefore differ from the nomenclature used by the authors in the article.

Source	Code	Effect	Comments
ref. 1 Cubero DI et al. Tegafur-uracil is a safe alternative for the treatment of colorectal cancer in patients with partial dihydropyrimidine dehydrogenase deficiency: a proof of principle. Ther Adv Med Oncol 2012;4:167-72. PubMed PMID: 22754590.	2 AS 1: AA	Four patients with colorectal cancer developed grade 3-4 toxicity after the first cycle of chemotherapy with fluorouracil (intravenous bolus of 425 mg/m^2 on days 1 and 5, in combination with folinic acid). They were found to be *1/*2A. After recovery, treatment with tegafur-uracil in combination with folinic acid was initiated. A full dose (100%) was tegafur 100 mg/m^2 three times daily for 21 days followed by a week-long rest period. Doses were rounded down to multiples of 100 mg tegafur. Doses were guided by adverse events. The first patient received 60% in the first cycle, 80% in the second cycle, 100% in the third cycle and 90% in the fourth and fifth cycles of the full dose of tegafur without development of grade 3-4 toxicity. This patient had developed grade 4 mucositis, diarrhoea and myelotoxicity on fluorouracil. The following 3 patients received 90% of the full dose of tegafur during 5 cycles without development of grade 3-4 toxicity in any of the cycles. Of the three patients, one developed grade 4 diarrhoea and grade 3 mucositis on fluorouracil, the second grade 3 diarrhoea and myelotoxicity, and the third grade 3 mucositis, diarrhoea and myelotoxicity. The best response in the first and the last patient, who both had metastatic disease, was achieving stable disease. The second and third patients receiving adjuvant chemotherapy were disease-free two years after the therapy.	Authors' conclusion: "Here, we demonstrate a complete absence of severe toxicity in all patients and cycles analysed. We believe that UFT is a safe alternative for the treatment of patients with partial DPD deficiency."
ref. 2 Deenen MJ et al. Standard-dose tegafur combined with uracil is not safe treatment after severe toxicity from 5-fluorouracil or capecitabine. Ann Intern Med 2010;153:767-8. PubMed PMID: 21135311.	2 AS 1: E AS 1.5: E	- One patient developed severe abdominal cramps, grade 4 diarrhoea, grade 4 neutropenia, dehydration and severe mucositis 10 days after initiation of capecitabine 1000 mg/m^2 BSA twice daily (in combination with oxaliplatin and bevacizumab). She recovered after discontinuation of capecitabine and 25 days at the hospital. A few months later she received tegafur-uracil 300 mg/m^2 per day in combination with folinic acid. After 10 days, she developed severe diarrhoea, mucositis, fever, dehydration and grade 4 neutropenia. She recovered after 25 days at the hospital. The patient was *1/*2A. - Three other patients requiring hospitalisation due to severe toxicity on fluorouracil or capecitabine therapy also developed severe toxicity following treatment with standard-dose tegafur-uracil. The patients were *1/*2A, *1/2846T and *1/1236A respectively. The DPD activity was approximately 50% in the latter two patients. This confirms that they were heterozygous and did not have a second unknown non-functional allele. The authors stated that tegafur-uracil is probably not safe in patients with partial DPD deficiency due to the greater effect of the DPD inhibitor uracil in these patients. They referred to an article that showed that uracil increases the half-life of fluorouracil to a greater extent in DPD-deficient patients, which leads to an increased risk of toxicity. The authors also stated that the tegafur dose in tegafur-gime-	Authors' conclusion: "The standard dose of UFT is not safe after severe toxicity to 5-FU or capecitabine in DPD-deficient patients."

ref. 2, continuation		racil-oteracil is 3x as low as in tegafur-uracil, while the DPD inhibitor is 200x more potent. However, fluorouracil is still metabolised by DPD after administration of tegafur-gimeracil-oteracil. This means that DPD also remains essential for detoxification of fluorouracil in this instance.	
ref. 3 SmPC Teysuno (tegafur/gimeracil/ oteracil) 11-04-18.	0 AS 0: E AS 1-1.5 + FENO: E	Contraindications: • Known dihydropyrimidine dehydrogenase (DPD) deficiency. • History of severe and unexpected reactions to fluoropyrimidine therapy. Pharmacodynamics: Mean 5-FU maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values were approximately 3-fold higher after Teysuno administration than after administration of tegafur alone, despite a 16-fold lower Teysuno dose (50 mg of tegafur) compared to tegafur alone (800 mg), and are attributed to inhibition of DPD by gimeracil. Maximum plasma uracil concentration was observed at 4 hours, with a return to baseline levels within approximately 48 hours after dosing, indicating the reversibility of DPD inhibition by gimeracil. Pharmacokinetics: In man, the apparent terminal elimination half-life (T1/2) of 5-FU observed after administration of Teysuno (containing tegafur, a 5-FU prodrug) was longer (approximately 1.6-1.9 hours) than that previously reported after intravenous administration of 5-FU (10 to 20 minutes). Following a single dose of Teysuno, 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. Interactions: Sorivudine or its chemically related analogues such as brivudine irreversibly inhibit DPD, resulting in a significant increase in 5-FU exposure. This may lead to increased clinically significant fluoropyrimidine-related toxicities with potentially fatal outcomes.	

Risk group	AS 1-1.5 and FENO with irreversible DPD inhibitors (uracil analogue antiviral drugs)

Comments:

- The article 'Deenen MJ et al. [Prevention of severe toxicity from capecitabine, 5-fluorouracil and tegafur by screening for DPD-deficiency]. Ned Tijdschr Geneeskd 2012;156:A4934.' has not been included, because the case in this article was already described in Deenen 2010.
- Existing guidelines:
  - Amstutz U et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther 2018;103: 210-6. PubMed PMID: 29152729.
    This guideline provides no dose recommendations for tegafur in combination with a DPD inhibitor. Tegafur is rated as a "no recommendation" (i.e. there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time).
    Tegafur with DPD inhibitor is not available in the United States. CPIC indicates, that for these therapies, evidence regarding the impact of gene variants on toxicity risk is very limited. Given the inhibition of DPD by the co-administered uracil or gimeracil, dose requirements of patients carrying decreased/no function DPYD variants are currently unknown.
    On 25-2-2019, there was not a more recent version of the guideline present on the PharmGKB- and on the CPIC-site.
  - Thorn CF et al. PharmGKB summary: fluoropyrimidine pathways. Pharmacogenet Genomics 2011;21:237-42. PubMed PMID: 20601926.
    The PharmGKB mentions four polymorphisms that are associated with toxicity (*2A, 496A>G, *5 and *9A). However, the latter two have not been associated with toxicity in studies and/or with reduced clearance or activity. These are therefore fully functional alleles.
    The PharmGKB writes that *2A has the highest association with fluoropyrimidine toxicity, although the frequency of this variant is less than 1% in Caucasians. The PharmGKB refers to an article that shows that the *2A allele does not always correlate with reduced DPD activity *in vivo*. Of the articles that found

increased risk of toxicity in patients with *2A, the PharmGKB only mentions the article from 2008 that showed that *2A has limited predictive capacity for severe fluorouracil toxicity. This capacity was more pronounced in male patients and with certain treatment protocols.
The PharmGKB concluded that the effect of *DPYD* gene on toxicity is clear. Given the low frequency of the variants, the unclear relationship between genotype and phenotype and the lack of diagnostic tests available before administration, the PharmGKB currently considers the effect not to be clinically relevant. More prospective studies are needed to investigate the influence of gender, treatment protocol, and additional unidentified DPYD variants on DPD-related toxicity.

Date of literature search: 12 February 2019.

	Phenotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	AS 0	0E	Yes	Yes	13 May 2019
	FENO	0E	Yes	Yes	
	AS 1	2E	Yes	Yes	
	AS 1.5	2E	Yes	Yes	

Mechanism:
Tegafur is mainly converted by CYP2A6 to fluorouracil. Fluorouracil is mainly (> 80%) converted by dihydropyrimidine dehydrogenase (DPD) to inactive metabolites. Lower metabolic activity of DPD leads to increased intracellular concentrations of fluorodeoxyuridine monophosphate, the active metabolite of fluorouracil. This leads to an increased risk of adverse events such as neutropenia and thrombocytopenia.
Tegafur is used in combination with the DPD inhibitor gimeracil (molar ratio 1:0.4) and was used in combination with the DPD inhibitor uracil (molar ratio 1:4). Both DPD inhibitors exhibit competitive inhibition of DPD. This is why efficacy is achieved at lower concentrations of the metabolites formed by DPD, which seem to contribute to the toxicity. Inhibition by DPD inhibitors is reversible and reduces over time.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to genotype the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	++
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	+++
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	+
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	
OR		
• Recommendation to genotype	++	++
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	

Total Score:	10+	8+
Corresponding Clinical Implication Score:		Essential