Dispensing oral temozolomide in children: precision and stability of a novel and ready-to-use liquid formulation in comparison with capsule-derived mixtures

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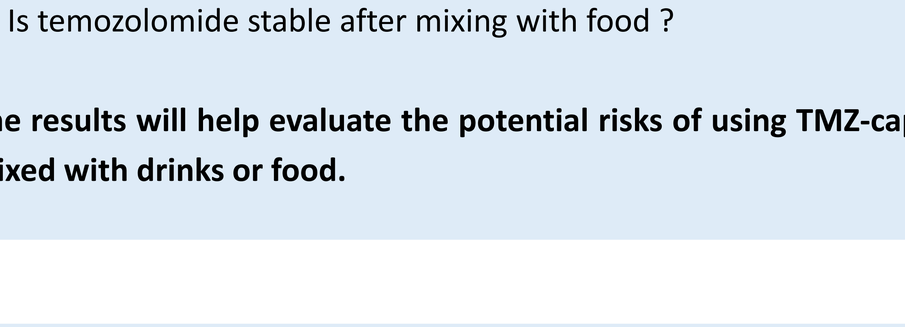
1.

RATIONALE

Kimozo® (temozolomide oral suspension)

- Currently, caregivers open Temodal® capsules and mix the content with soft food prior to administration to children[1].
- ORPHELIA developed Kimozo®, the first ready-to-use liquid pediatric formulation of temozolomide (TMZ).
  - ✓ Ready-to-use, age-adapted formulation (oral suspension)
  - ✓ Bioequivalent to Temodal®
  - ✓ High drug load (40mg/mL), accurate dose (4mg)
  - ✓ Taste-masked
  - ✓ Long-term stability at 2-8°C (≥ 24 months)
  - ✓ Avoid caregiver exposition to the cytotoxic drug
  - ✓ A « Pediatric Quality Target Product Profile »
- This study aimed at assessing the risks associated with handling of temozolomide (TMZ) capsules in comparison with a ready-to-use oral suspension specifically formulated for children.



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OBJECTIVES

Parents and caregivers overcome the lack of commercially available pediatric formulations by mixing adult dosage forms with food.

The objective of the study is to assess the amount of TMZ effectively dispensed using such capsule-mixing protocols, as a percentage of the nominal amount and to assess the stability of TMZ in various food matrices. Results will be compared to the amount of TMZ dispensed with KIMOZO ready-to-use oral suspension.

Questions:

- Do you deliver the accurate dose of temozolomide to children ?
- Is temozolomide stable after mixing with food ?

The results will help evaluate the potential risks of using TMZ-capsules mixed with drinks or food.

3.

MATERIAL & METHODS

Protocol

90 mg of TMZ (average dose used for a child under the age of 6) were prepared using 4 capsules of 20 mg and 2 capsules of 5 mg of Temodal® (and compared with 2.2 mL of Kimozo®, equivalent to 88 mg of TMZ).

Accuracy measurement: Temodal® capsules were mixed with 100 g/mL of apple sauce/juice, stirred for 30 seconds, transferred to a volumetric flask containing an acidic solution and centrifugated for dosage. The experiments were carried out 3 times by 6 non-analyst operators.

Stability testing: Temodal® capsules were mixed at room temperature with different children food matrices (100 g) : apple sauce, chocolate cream, mash potatoes and infantile milk. TMZ was left in contact with food matrices for 0, 30 & 60 min, then transferred to a volumetric flask containing an acidic solution and centrifugated for dosage. The experiments were carried out 3 times.

TMZ and its degradation product, amino-imidazole-carboxamide (AIC), were assayed using UV-HPLC at 0, 30 and 60 min. Statistical analysis was performed to evaluate TMZ recovery, AIC amount and impact of operator on accuracy. pH was also measured. Acceptance criteria were pre-defined for TMZ (95-105%) and AIC (<1%) content.

4.

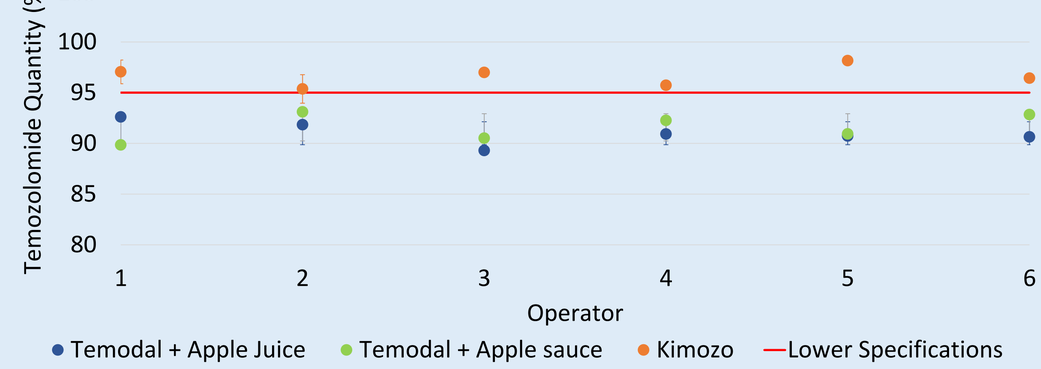
RESULTS

Accuracy

When dispensing Temodal® capsules, the delivered dose of TMZ is systematically under the lower specifications of 95%, whether using apple sauce (mean dose = 91.6%, range = 90-93%) or apple juice (mean = 91.0%, range = 89-93%).

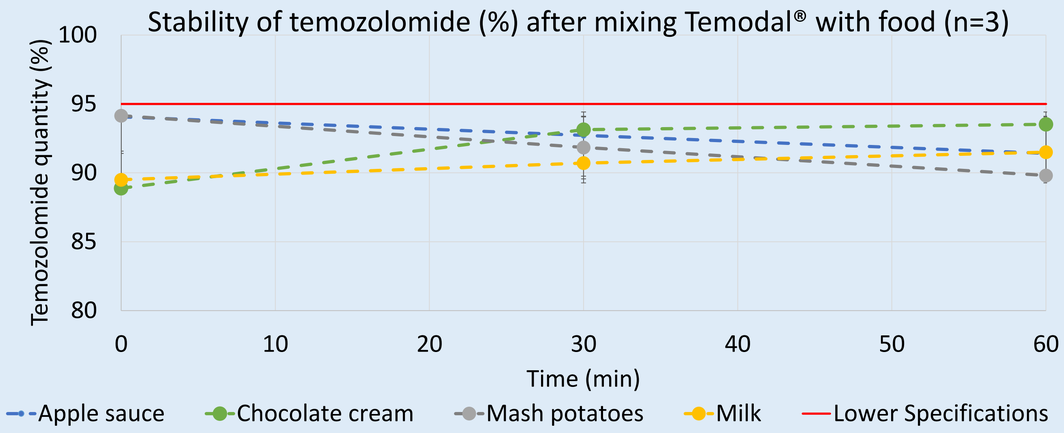
When using Kimozo®, the delivered dose is always within specifications (mean dose = 96.6%, range = 95.4-98%).

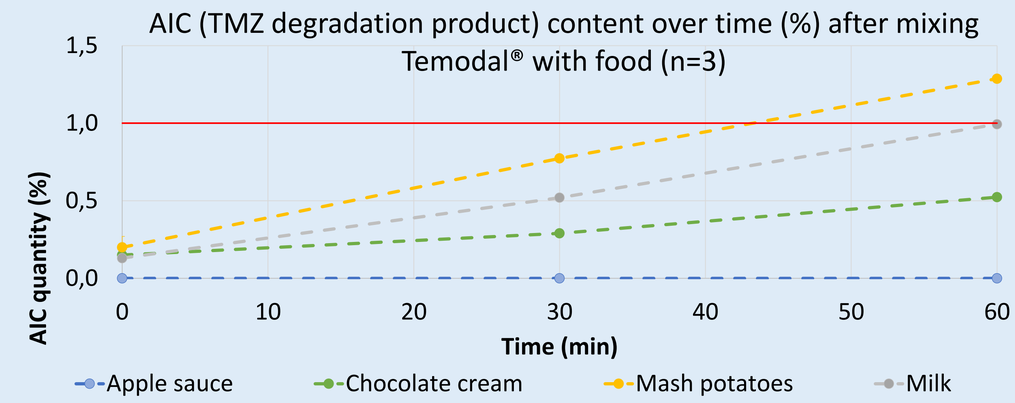
Delivered dose after mixing Temodal® capsules with food in comparison to ready-to-use Kimozo®



Chemical and physical stability

The 4 tested food vehicles (apple sauce, chocolate cream, infantile milk, mash potatoes) had a significant effect on TMZ stability (p=0.0042) and AIC significantly increased over time in 3 of the 4 vehicles (p<0.0001). Degradation of TMZ is probably related to the pH of the matrix (from 6.4 to 6.8 for mash potatoes, chocolate cream and milk. Poor homogeneity after mixing is also observed in certain food vehicles,





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CONCLUSIONS

Temodal® dispensed with food using a spoon is systematically underdosed (poor recovery and instability), whereas Kimozo® delivers the right dose (≥ 95% of nominal). In our experiment, only 1/72 preparations from Temodal® capsules in food met the acceptance criteria.

Taking into account the known food effect (mean AUC_{0-24} decreased by 9%)[2], **our experiments suggest that mixing Temodal® capsule content with food may result in significant underexposure**.

Kimozo® offers a viable alternative with a better dosage accuracy.

6.

REF.

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