Public Assessment Report
for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Temesta/ Tavor/Ativan

(Lorazepam)

BE/W/0010/pdWS/01

Marketing Authorisation Holder: Pfizer

Rapporteur:	Belgium
Finalisation procedure (day 120):	20/08/2020

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Temesta/ Tavor/ Ativan
INN (or common name) of the active substance(s):	Lorazepam
MAH:	Pfizer
Currently approved Indications for *Ativan* (UK SmPC)	IV - Pre-operative medication or premedication for uncomfortable or prolonged investigations, e.g. bronchoscopy, arteriography, endoscopy. - The treatment of acute anxiety states, acute excitement or acute mania. - The control of status epilepticus.
Pharmaco-therapeutic group (ATC Code):	N05BA06
Pharmaceutical form(s) and strength(s):	Intravenous form of lorazepam

I. EXECUTIVE SUMMARY

SmPC changes are proposed in Sections 4.1, 4.2, and 5.2 (and corresponding PIL sections).

II. RECOMMENDATION

Based on the submission of paediatric clinical data on the use of lorazepam IV in status epilepticus and on the review of literature performed in this context, it is recommended

- for MSs which already have a paediatric indication for the treatment of status epilepticus to update: the applicant is requested to update the paediatric information in Sections 4.1, 4.2 and 5.2 of the SPC via a national type II variation (see section V).

- for MSs which don't have the paediatric indication of status epilepticus, the applicant is recommended to submit a national type II variation to extend the indication (see section V).

III. INTRODUCTION

On 27 April 2017, the MAH submitted a completed paediatric study for Temesta IV, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.
A short critical expert overview has also been provided.
The MAH stated that the submitted paediatric study does not influence the benefit risk for Temesta and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

The **intravenous form of lorazepam** was used in this study: (strengths: 4 mg for adults and 0.05 mg/kg for children).

IV.2 Clinical aspects

1. Introduction

The MAH submitted the final report for Study B3541002 evaluating the efficacy and safety of lorazepam intravenously administered in adult and paediatric subjects with Status Epilepticus or Repetitive Status Epilepticus.

2. Clinical study

Study B3541002: "A Multi-Center, Open-Label, Non-Controlled Study to Evaluate the Efficacy and Safety of Lorazepam Intravenously Administered in Subjects With Status Epilepticus or Repetitive Status Epilepticus."

➢ Description

Study B3541002 was a multi-center, open-label, non-controlled study in Japanese patients with status epilepticus (SE) or repetititve SE, conducted in 15 centers in Japan.

➢ Methods

- Objectives

- The primary objective was to evaluate the efficacy and safety of lorazepam intravenously (IV) administered in subjects with status epilepticus (SE).
- The secondary objective was to evaluate the pharmacokinetics (PK) of lorazepam in Japanese subjects with SE.

- Study design

This was a multi-center, open-label, non-controlled study in Japanese subjects with SE or repetitive SE.
This study had up to a 6-month screening period, up to a 2-day treatment period and follow-up visit 7 days after the last administration.

- Diagnosis and Main Criteria for Inclusion

Subjects (either gender) >3 months of age with SE or repetitive SE/cluster seizures who had seizures that could have been evaluated by investigator's visual observations based on motor symptoms or who had seizures that could be evaluated by EEG were enrolled in this study.

Main exclusion criteria: Subjects with known or suspected recurrent seizures due to illegal drug or alcohol withdrawal, hypersensitivity to lorazepam or benzodiazepine, or benzodiazepine abuse.

- Study population /Sample size

The target number of subjects with SE or repetitive SE/cluster seizures who had seizures that could be evaluated by the investigator's visual observations based on motor symptoms was approximately **25** (including at least 3 adult subjects).
At least 3 subjects were to be enrolled in the category of nursing infants with the lower age limits 3 months to <1 year. In addition, at least 3 subjects were to be enrolled in the combined categories of infants (1 year to <7 years) and children (7 years to <16 years).
At least 5 adult subjects (including at least 3 with motor symptoms) with SE or repetitive SE/cluster seizures who had seizures that could be evaluated by electroencephalogram (EEG) were to be enrolled. The subjects were classified based on age at the initial administration of the study drug.

- Treatments

- For adult subjects (>16 years), **lorazepam 4 mg** was administered as a slow IV injection at a rate of approximately 2 mg/minute.
- For pediatric subjects (3 months to <16 years**), lorazepam 0.05 mg/kg** (but not exceeding 4 mg) was administered as a slow IV injection at a rate of approximately 2 mg/minute.

For subjects whose seizure did not stop or stopped but recurred within 10 minutes after the initial dose, the second dose could be administered at the same dose and injection rate as the

initial dose, at least 10 minutes after the initial dose. For subjects whose seizure stopped but recurred >10 minutes after the initial dose (but within 12 hours of the initial dose), an additional dose could be administered at the same dose and injection rate as the initial dose. A total of 2 doses were permitted in this study.

- Outcomes/endpoints

Primary Efficacy Evaluation:
Proportion of subjects whose seizures stopped within 10 minutes after initial dose and who continued seizure-free for at least 30 minutes after the completion of initial dose (efficacy rate).

Secondary Efficacy Evaluations:
Key Secondary Efficacy Evaluation:
Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 30 minutes.

Secondary Efficacy Evaluations:
 (1-1) Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (only the initial dose) and who continued seizure-free for at least 12 hours postdose;
 (1-2) Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 12 hours postdose;
 (2-1) Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (only the initial dose) and who continued seizure-free for at least 24 hours postdose;
 (2-2) Proportion of subjects whose seizures stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and who continued seizure-free for at least 24 hours postdose;
 (3-1) Time to resolution of seizures from the administration of study drug (only the initial dose);
 (3-2) Time to resolution of seizures from the administration of study drug (either initial or second dose);
 (4-1) Time to relapse from the resolution of seizures following the administration of study drug (only the initial dose, within 24 hours);
 (4-2) Time to relapse from the resolution of seizures following the administration of study drug (either initial or second dose, within 24 hours).
For each of the above endpoints, stop (resolution) of seizures during the IV administration of study drug was also considered as stop (resolution) of seizures for the endpoint.

Pharmacokinetic and Pharmacogenomic Evaluations:
-Pharmacokinetics: Blood samples (2 mL, or 1 mL for subjects who had difficulties) to provide a minimum of 0.5 mL plasma for PK analysis were collected into appropriately labeled tubes containing ethylenediaminetetraacetic acid at the times described below:
 One (1) sample was to be taken between immediately after and 10 minutes after completion of initial dose, 1 sample between 30 minutes and 2 hours after completion of initial dose (specified at the time of initial dose regardless of presence/absence of second dose), and 2 samples between 12 hours to 48 hours after final dose at an interval of 12 hours or longer;
 Even if the drug was switched to other treatment, blood samples were to be collected at

the specified time.
Plasma samples were analyzed for lorazepam concentrations using validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric method.
-Pharmacogenomics: Uridine diphosphate glucuronosyl transferase 2B15 (UGT2B15) genotyping (*1/*1, *1/*2 or *2/*2) was performed in this study. Two (2) buccal swab samples were collected from each subject who agreed to sample collection for pharmacogenomic analysis between treatment and follow-up period. Samples were analyzed using a validated analytical method.

Safety Evaluations:
Safety evaluations included clinical monitoring, physical examination, vital signs (heart rate, blood pressure), oxygen saturation, adverse events and safety laboratory tests.

- Statistical Methods

Efficacy: The primary analysis population was the full analysis set defined as all subjects who received at least 1 dose of study drug, and excluded subjects whose SE or repetitive SE/cluster seizures was determined by the EEG. The 95% confidence intervals (CIs) were calculated based on the exact CI by the Clopper-Pearson method. For the efficacy rate in the endpoint, the point estimate and 95% CI were presented. For the endpoints of the time resolution of seizures or relapse, the time was descriptively summarized and Kaplan Meier estimates of the time to resolution of seizure or relapse was provided. The efficacy endpoints were presented in subgroups of adult or pediatric subjects; however, 95% CIs were not to be calculated in these subgroups. For the subjects with SE or repetitive SE/cluster seizures who had seizures which were evaluated by EEG, the data were listed by subject.

Pharmacokinetics: The PK analysis set consisted of subjects who received lorazepam and measured plasma lorazepam concentrations. The concentrations and the sampling time from the end of test drug administration were summarized according to the time windows below.
1. Between immediately after and 10 minutes after completion of the initial dose;
2. Between 30 minutes and 2 hours after completion of the initial dose (for single dose);
3. Between immediately after and 1 hour 50 minutes after completion of the last dose (for second dose);
4. Between 12 hours and 18 hours after completion of the last dose (included 18 hours);
5. Between 18 hours and 24 hours after completion of the last dose (included 24 hours);
6. Between 24 hours and 36 hours after completion of the last dose (included 36 hours);
7. Between 36 hours and 48 hours after completion of the last dose.

Pharmacogenomics: Frequency of each UGT2B15 genotype was tabulated.
Safety: The safety data were summarized based on the safety analysis set (SAS) which consisted of all subjects who received at least 1 dose of study drug. The subjects who were enrolled as subjects with SE or repetitive SE/cluster seizures who had seizures which were evaluated by EEG were included in SAS. The safety was analysed according to the algorithm and formats that were specified according to the sponsor data standards. The last measurement before first dose was defined as baseline. The safety endpoints were presented in subgroups of adult or paediatric subjects.

➢ Results

• Subject Disposition

A total of 26 subjects were enrolled in the study and treated. All subjects completed the study. One subject was excluded from the efficacy analysis due to SE seizures that were evaluated by EEG. All subjects were analysed for safety.
Of the 26 subjects, **10** (38.5%) were **adult** with mean age 27.6 years while **16** (61.5%) were from **pediatric** population with mean age of 5.4 years.

• PK results

In table 1 plasma lorazepam concentrations versus time are shown. The mean maximum concentration (within 10 minutes of dosing) was 119.4 ng/mL. At first sight, there was no difference between mean Cmax values in adults and children, however, no statistical analysis has been performed. One plasma sample from a pediatric subject had a very high lorazepam concentration (3800 ng/mL) at 11 minutes after the second dose. No definitive cause for this high concentration was identified. The validity of the assay was confirmed by the incurred sample reproducibility assessment.

Table 1: Plasma lorazepam concentration (ng/mL) versus time

	Time Window After End of Initial Dose						
	Within 10 Minutes	**0.5-2 Hours[a]**	**Within 1 Hour 50 Minutes[b]**	**12-18 Hours**	**18-24 Hours**	**24-36 Hours**	**36-48 Hours**
All enrolled subjects							
N/NALQ	23	13	10	12	12	4	23
Mean	119.4	42.94	460.0	25.44	24.34	13.71	10.15
SD	146.34	15.287	1174.0	13.375	13.321	4.2413	8.5011
Min	9.33	29.4	49.3	11.9	9.65	7.54	1.56
Max	566	69.1	3800	56.3	42.7	16.9	29.8
Adult subjects							
N/NALQ	8	6	2	6	3	4	7
Mean	128.3	53.13	102.7	28.03	40.97	13.71	14.11
SD	150.33	17.642	13.223	9.7377	1.5177	4.2413	8.7798
Min	15.3	30.4	93.3	18.2	39.6	7.54	4.57
Max	489	69.1	112	41.5	42.6	16.9	29.8
Paediatric subjects							
N/NALQ	15	7	8	6	9	-	16
Mean	114.7	34.20	549.4	22.85	18.79	-	8.409
SD	149.28	3.8743	1314.0	16.811	10.254	-	8.0371
Min	9.33	29.4	49.3	11.9	9.65	-	1.56
Max	566	40.4	3800	56.3	42.7	-	28.6

Source: B3541002 CSR Report Body Table 13
Summary statistics had been calculated by setting concentration values below the lower limit of quantification to 0. Summary statistics were not presented if NALQ=0.
Abbreviations: Max=maximm; min=minimum; N=number of observations (non-missing concentrations); NALQ=number of observations above lower limit of quantification; SD=standard deviation.
a. For subjects who only received the initial dose.
b. For subjects who received the second dose.

- **Efficacy results**

- Primary Endpoint

A total of 12 subjects (48.0%) had initial seizure stopped within 10 minutes and continued seizure-free for at least 30 minutes after the completion of initial dose. **The lower bound of 95% CI of the primary efficacy endpoint was lower than 30% (pre-specified expected minimum efficacy rate).**

- Key Secondary Endpoint:

A total of 16 subjects (64.0%) had initial seizure stopped within 10 minutes after the administration of study drug (either initial or second dose [in 10 to 30 minutes from the initial dose]) and continued seizure-free for at least 30 minutes.

- Other secondary endpoints:

- Time to Resolution of Seizures From the Administration of Study Drug

Median time for the resolution of the seizures was 1 minute for overall population in subjects with initial dose as well as subjects with either dose (initial or second dose).

- Time to Relapse From the Resolution of Seizures Following the Administration of Study Drug.

Median time for the relapse of the seizures was 62 minutes for the overall population in subjects with initial dose while 103 minutes for subjects with either initial or second dose.

- **Safety results**

A total of 12 subjects (46.2%) experienced 17 TEAEs of which 4 TEAEs were reported as treatment-related.
The majority of TEAEs were mild or moderate in severity. One TEAE of pneumonia aspiration was considered severe.
No treatment-emergent death was reported in this study. One treatment-emergent serious adverse event of pneumonia aspiration was reported, but it was considered not to be related to treatment. No permanent or temporary discontinuations were reported in the study.
The most common TEAEs by preferred term were **somnolence** (2 TEAEs) and **insomnia** (2 TEAEs).

3. Discussion on clinical aspects

Efficacy

The primary efficacy endpoint of this study (proportion of subjects whose seizures stopped within 10 minutes after initial dose and who continued seizure-free for at least 30 minutes after the completion of initial dose) was not achieved since the lower bound of 95% CI was lower than 30% (pre-specified expected minimum efficacy rate).
Explanation of this low efficacy rate by the MAH:
Because the study required detailed informed consent, this probably led to the enrolment of subjects experiencing frequent SE or the subjects who suffered from intractable diseases resistant to treatment. The investigator confirmed that many of the subjects for this study had specified medical histories related to intractable epilepsy or other diseases. However, the key secondary endpoint, which included the subjects who received the second dose achieved a higher efficacy rate of 64%.

Pharmacokinetics
Concerning the secondary objective (assessment of the pharmacokinetics of lorazepam in Japanese subjects with SE) sample sizes included in this study were too small to draw any conclusions.

Safety
Safety results of the study are generally in line with the current product information. No new safety issue emerged from this study.

V. OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

No firm conclusion can be drawn from this small open-label, non-controlled study in Japanese patients. Therefore the benefit-risk profile of IV lorazepam in the treatment of status epilepticus in children is considered unchanged.

As requested, the MAH has performed a literature review of treatment of status epilepticus to evaluate if an harmonization of this indication and paediatric dosage was necessary throughout the SmPC of the different Member States.
Lorazepam IV is internationally recognized as a first-line treatment of SE in children and adults when an IV access is available.
Considering the dose of lorazepam IV used to treat convulsive SE, most of the guidelines and publications mention a paediatric dose of 0.1 mg/kg.

In addition, the MAH also reviewed published pharmacokinetic data, showing that lorazepam pharmacokinetic parameters in paediatric subjects (3 months to <16 years) are within the range reported in adults, except for increased clearance. Weight adjusted CL and Vd tend to be higher in younger infants and children compared to older children, but these differences do not appear to be statistically significant. However, in vivo data and PBPK modelling indicated that neonates require substantially lower doses than suggested for infants and children.

➢ Recommendation

- **For MSs which already have the paediatric indication of status epilepticus**, the following wording should be implemented by a national type II variation submitted within 60 days after the end of the procedure:

1. Proposed change in section 4.1. of the SmPC:

- Lorazepam IV is indicated in the control of the status epilepticus in adults, adolescents, children and infants from 1 month of age.

2. Proposed changes in section 4.2 of the SmPC:

Paediatric population (children and infants from 1 month of age)

- 0.1 mg/kg.
- Maximum 4mg/dose

If seizures persist within the next 10-15 minutes, the same dose may be injected again but no more than 2 doses should be given.

3. If necessary, **section 4.3.** should be adapted accordingly to the updated paediatric indication and posology.

4. It is proposed to add (if not yet present) or clarify the following information in section 5.2 of the SmPC:

Absorption: {lorazepam}Injection is readily *and about completely* absorbed when given intramuscularly. Peak plasma concentrations occur approximately 60-90 minutes following intramuscular administration.

Distribution: Following intravenous administration, the mean volume of distribution is approximately 1.3 litres/kg. Unbound lorazepam penetrates the blood/brain barrier freely by passive diffusion. Lorazepam is approximately 92% bound to human plasma proteins at lorazepam concentration of 160 ng/ml.

Metabolism: {lorazepam} is metabolised by a simple one-step process to a pharmacologically inactive glucuronide. There is minimal risk of accumulation after repeated doses, giving a wide margin of safety. The total clearance of lorazepam following intravenous dose is about 1.0-1.2 ml/min/kg.

There are no major active metabolites.
Based on in vitro studies, multiple UGT enzymes contribute to the hepatic glucuronidation of R- and S-lorazepam. Both R- and S-lorazepam were glucuronidated by UGT2B4, 2B7, and 2B15; additional hepatic and extrahepatic UGT enzymes also metabolized both R- and S-lorazepam in vitro.

Elimination: The elimination half-life is about 12-16 hours when given intramuscularly or intravenously. Following a single 2 mg and 4 mg intravenous dose of lorazepam to small groups of healthy subjects (n=6 and n=7 subjects, respectively),cumulative urinary excretion of lorazepam glucuronide was estimated to be more than 80% of the dose.

Special Populations

Effect of Age/ Paediatrics: Neonates (Birth to 1 month): Following a single 0.05 mg/kg (n=4) or 0.1 mg/kg (n=6) intravenous dose of lorazepam, mean total clearance normalised to body-weight was reduced by 80% compared to normal adults, terminal half-life was prolonged 3-fold, and volume of distribution was decreased by 40% in neonates with asphyxia neonatorum compared to normal adults. All neonates were of ≥37 weeks of gestational age.

There was no significant age-related difference in body-weight normalised clearance in children, adolescents and adults observed in 50 children from 2.3-17.8 years old. Population pharmacokinetic analyses for paediatric patients (except neonates) also suggested similar pharmacokinetics to adults.

Effect of Age/ Elderly: Following single intravenous doses of 1.5 to 3 mg of lorazepam injection, mean total body clearance of lorazepam decreased by approximately 20% in elderly subjects compared to younger adults.

Effect of Gender: Gender has no effect on the pharmacokinetics of lorazepam.

Renal Insufficiency: Single-dose pharmacokinetic studies in patients with degrees of renal insufficiency ranging from mild impairment to renal failure have reported no significant changes in absorption, clearance, or excretion of lorazepam. Haemodialysis did not have any significant effect on the pharmacokinetics of intact lorazepam, but substantially removed the inactive glucuronide from the plasma.

Hepatic Disease: No change in the clearance of lorazepam was reported in patients with mild to moderate hepatic impairment (ie, hepatitis, alcoholic cirrhosis).

5. Excipients:
When applicable, the applicant is requested to implement revised warnings for benzyl alcohol and propylene glycol within the next 3 years.
Reassurance with regards to excipients in the SmPC/PIL may be required (considering the dose and duration of treatment, the warnings might be alarming and lead to confusion or possible delays in treatment).

6. Update of PL:
The MAH should update the PL accordingly to the a-m proposed SmPC changes

- **In MSs which don't have the indication yet,** the MAH is strongly encouraged to submit a national type II variation to add the paediatric indication of status epilepticus, with the totality of all paediatric evidence provided in the scope of this PdWS together with the updates of the SmPC and PIL discussed in this procedure.
  The type II variation should be submitted within 60 days of the final AR.