CBG MEB

# Public Assessment Report

# Scientific discussion

# Sunitinib Teva 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules

# (sunitinib)

## NL/H/3718/001-004/DC

## Date: 31 July 2018

**This module reflects the scientific discussion for the approval of Sunitinib Teva 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules . The procedure was finalised on 10 January 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| ERA | Environmental Risk Assessment |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sunitinib Teva 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules from Teva B.V.

The product is indicated for:

- the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.
- the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.
- the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Sutent 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules (EU/1/06/0347) which has been registered through a centralised procedure in the EEA by Pfizer Ltd since 19 July 2006.

The concerned member states (CMS) involved in this procedure were:

- *Sunitinib Teva 12.5 mg* - Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovak Republic and United Kingdom.
- *Sunitinib Teva 25 mg* – Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Italy, Luxembourg, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovak Republic and United Kingdom.
- *Sunitinib Teva 37.5 mg* – Austria, Belgium, Cyprus, Germany, Denmark, Greece, Spain , Finland, Croatia, Hungary, Italy, Luxembourg, Norway, Poland, Portugal, Sweden, Slovenia and United Kingdom
- *Sunitinib Teva 50 mg* - Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovak Republic and United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

- Sunitinib Teva 12.5 mg is a hard gelatin capsule with a medium orange opaque cap and medium orange opaque body imprinted with “12.5” in black ink on the cap. Each capsule contains 12.5 mg sunitinib.
- Sunitinib Teva 25 mg is a hard gelatin capsule with a light orange opaque cap and medium orange opaque body imprinted with “25” in black ink on the cap. Each capsule contains 25 mg sunitinib.
- Sunitinib Teva 37.5 mg is a hard gelatin capsule with a rich yellow opaque cap and rich yellow opaque body imprinted with “37.5” in black ink on the cap. Each capsule contains 37.5 mg sunitinib.
- Sunitinib Teva 50 mg is a hard gelatin capsule with a light orange opaque cap and light yellow opaque body imprinted with “37.5” in black ink on the cap. Each capsule contains 50 mg sunitinib.

All capsules contain an orange granulated powder.

The hard capsules are packed in high-density polyethylene (HDPE) bottles with a polypropylene (PP) child resistant closure and PVC/Aclar/PVC/Aluminium foil blisters.

The excipients are:
*Capsule content* - mannitol, povidone K-25, croscarmellose sodium and magnesium stearate
*Capsule shell* – gelatin, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172)(only 12.5 mg, 25 mg and 50 mg)
*Printing Ink* – shellac, black iron oxide (E172), propylene glycol, concentrated ammonia solution and potassium hydroxide

## II.2 Drug Substance

The active substance is sunitinib base, an established active substance not described in any Pharmacopoeia. The active substance is a yellow to orange crystalline powder which is not hygroscopic. The solubility in aqueous solution is pH dependent; below a pH of 6 sunitinib base is soluble in aqueous solution whereas above pH 7 it is only sparingly soluble in water. Several forms (>30) of sunitinib base are known in the literature. The process followed by the MAH consistently produces sunitinib base of form III, which form is stable when exposed to extreme humidity, temperature and mechanical conditions.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of sunitinib consists of four synthetic steps and a final purification step. No class I organic solvents or heavy metal catalysts have been used. The active substance has been adequately characterised and acceptable specifications have been adopted for the used solvents and reagents.

Quality control of drug substance
The active substance specification has been established in-house by the MAH. It is considered adequate to control the quality and is acceptable in view of the route of synthesis and the various European guidelines. Analytical data demonstrating compliance with this specification have been provided for 5 production scale batches.

Stability of drug substance
Stability data on the active substance(s) have been provided for 3 full scale batches stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (6 months). No clear up- or downward trends have been observed under accelerated or long term conditions. Therefore, the proposed retest period of 36 months, with the storage condition "Store in the original packaging" is acceptable.

## II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The aim of the formulation development was to obtain a robust, stable, immediate release formulation containing quantitatively the same active substance as the reference product. Different manufacturing processes were considered in early development, and on the basis of these studies wet granulation was selected for final production. Furthermore, optimisation of the formulation was done to justify the amount of excipients selected. The pharmaceutical development of the product has been adequately performed, and the choices of the packaging and manufacturing process have been justified.
Two bioequivalence studies were performed between Sunitinib Teva 12.5 mg and 50 mg, hard capsules and Sutent 12.5 mg and 50 mg hard capsules. For the other two strengths a biowaiver has been requested. Hence, comparative dissolution studies with the biobatches of the test product versus

the biobatches of the reference product were performed at 3 pH's (0.1 N HCl (pH ~1.2), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). Only in 0.1 N HCl comparable dissolution was demonstrated, at pH 4.5 and 6.8 the dissolution profiles were not comparable, however, as bioequivalence has been shown *in vivo*, and the differences have been justified by the difference in solubility between Sunitinib base (test product) and Sunitinib Malate (reference product), this can be accepted. Similarity between the dissolution profiles of the 50 mg biobatch and the 25 mg & 37.5 mg strengths, has been shown at 3 pH's (0.1 N HCl (pH ~1.2), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The process consists of the following phases: granulation phase, milling of the granules and mixing with external phase, encapsulation of the final blend into the hard capsules, and packaging of the capsules. The product is manufactured using conventional manufacturing techniques. Process validation for full scale batches will be performed post authorisation.

Control of excipients
The excipients mannitol, povidone K-25, croscarmellose sodium, magnesium stearate and water purified comply with the Ph. Eur. requirements. These specifications are acceptable, as well as the specification of the hard gelatin capsules.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description of capsule and capsule content, identification, uniformity of dosage units (by content uniformity), assay, impurities, dissolution and microbiological examination. The release and shelf-life requirements/limits are identical. The limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data for 2 batches per strength, packaged in two different packaging materials, providing a total of 16 batch analyses, from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 2 batches per strength stored at 25°C/60% RH (6 batches for 24 months and 2 batches for 18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed blisters and bottles. Photostability studies were performed in accordance with ICH and showed that the product is stable when exposed to light. As no clear up- or downward trends are observed in the provided stability data under long term and accelerated conditions, the proposed shelf-life of 24 months can be accepted. Based on the provided stability data no special storage conditions regarding temperature and humidity are required. However, the storage condition: "*Do not store above 30 °C. Store in the original packaging to protect from moisture*." can be accepted, as this will not require special storage for the users. In-use stability data have been provided demonstrating that the product remains stable for 30 days following first opening of the container, without special storage conditions. However, no in-use stability is provided in the SmPC, as it has been justified that this is not required.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM have been provided for the used gelatin and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sunitinib Teva has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

# III. NON-CLINICAL ASPECTS

## III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sunitinib Teva is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

## III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Sutent which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

Sunitinib is a well-know active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which is discussed below.

## IV.2 Pharmacokinetics

Biowaiver
A biowaiver for a bioequivalence study for additional lower strengths (25 and 37.5 mg) of sunitinib is applied for by the MAH. According to sunitinib product-specific guidance (EMA/CHMP/315233/2014), the pharmacokinetics for sunitinib is linear, thus the request of the biowaiver might be acceptable for the lower strengths.
For Sunitinib Teva, all products were manufactured by the same process and the composition of the different strengths is qualitatively the same. The proportional amount of excipients is contained in strengths, which is considered acceptable. Thus the composition of the strengths (i.e. 25 mg, 37.5 mg and 50 mg) is dose proportional.
Both test and reference product contain mannitol in all strengths, which may affect absorption from the gastrointestinal tract. Comparative bioavailability studies have shown that mannitol is considered to not affect the absorption of sunitinib. Thus criteria for requesting the biowaiver for additional strengths are met.
The dissolution data of Sunitinib Teva 25 mg, 37.5 mg and 50 mg, hard capsules have been presented. At pH 1.2 and 4.5, capsules from all three strengths dissolved more than 85% within 15 minutes. For pH 6.8, F2 value for both lower strengths is greater than 50 compared with the 50 mg capsules. Overall, similarity in dissolution has been demonstrated at the three requested pH levels between the lower strengths (25 mg and 37.5 mg) and the 50 mg strength of Sunitinib Teva.
Therefore, the conclusion of the BE study with the sunitinib 50 mg strength can be extrapolated to the lower strengths of 25 mg and 37.5 mg capsules.

Bioequivalence studies
The MAH conducted two bioequivalence studies:

- The pharmacokinetic profile of the test product Sunitinib Teva 12.5 mg, hard capsules (Teva Nederland B.V., NL) compared with the pharmacokinetic profile of the reference product Sutent 12.5 mg hard capsules (Pfizer Ltd, UK).

- The pharmacokinetic profile of the test product Sunitinib Teva 50 mg, hard capsules (Teva Nederland B.V., NL) compared with the pharmacokinetic profile of the reference product Sutent 50 mg hard capsules (Pfizer Ltd, UK).

The choice of the reference product in the bioequivalence studies is accepted, as Sutent has been registered trough a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

In general, for an immediate release formulation of a substance indicated to be taken with or without food intake, a single dose study under fasting conditions using the highest strength (i.e., 50 mg for sunitinib) is considered appropriate. Such a study design is also in line with the Sunitinib Product-specific Bioequivalence Guidance (EMA/CHMP/315233/2014). However, the guidance is referring to sunitinib maleate as active pharmaceutical ingredient in Sutent while Sunitinib Teva capsules contain sunitinib base. Sunitinib base is less soluble than sunitinib maleate at pH 6.8, thus although the comparative bioavailability study was conducted under fasting condition, in addition the effect of food on drug absorption was studied with the 50 mg capsules.

Taking into account the difference in quantitatively composition between 12.5 and 50 mg strength an additional bioequivalence study was performed with Sunitinib Teva capsules 12.5 mg vs. Sutent 12.5 mg in fasting conditions. An addition of a fed arm in the study with 12.5 mg strength was not considered necessary because according to section on Bracketing approach in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), in case of deviation from proportional composition it is sufficient to assess bioequivalence in both fasting and fed state at only one of the strengths, and the highest strength of 50 mg is considered to be the most sensitive strength for comparison of PK profile of sunitinib in both fasting and fed conditions in the light of PK linearity of sunitinib.

The designs of both studies are acceptable.

*Analytical/statistical methods*
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

**Bioequivalence study I – 12.5 mg sunitinib**
*Design*
A monocentric, open label, block randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 18 healthy male and female subjects, aged 30 ± 9 years. Each subject received a single dose (12.5 mg) of one of the 2 sunitinib formulations. The capsule was orally administered with 240 ml water after at least 10 hours of fasting. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 24, 36, 48 and 72 hours after administration of the products.

*Results*
One subject was withdrawn due to concentrations under lower limit of quantification and one subject withdrew due to a personal schedule conflict. Therefore, 16 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of sunitinib under fasted conditions.

| **Treatment N=16** | **$AUC_{0-72}$** ng/ml/h | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|
| **Test** | 214.2 ± 56.8 | 6.04 ± 1.55 | 7.0 (5.0-13.0) |
| **Reference** | 227.3 ± 51.4 | 6.20 ± 1.24 | 7.5 (5.0-11.0) |
| **Ratio (90% CI)** | 0.93 | 0.96 | -- |

| | | | |
|---|---|---|---|
| | (0.89 - 0.97) | (0.93 - 1.00) | |
| **Intra-subject variability** | 7.5% | 5.8% | -- |
| **$AUC_{0-72}$** area under the plasma concentration-time curve from time zero to 72 hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration<br>**CV** coefficient of variation | | | |

**ln-transformed values*

**Bioequivalence study I – 50 mg sunitinib**

*Design*

A monocentric, open label, block randomised, two-treatment, three-period, six-sequence, single dose, crossover bioequivalence study was carried out under fasted and fed conditions in 18 healthy male and female subjects, aged 33 ± 8 years. Each subject received a single dose (50 mg) of one of the 2 sunitinib formulations. The capsule was orally administered with 240 ml water after at least 10 hours of fasting or after the start of serving of a standardised high-fat, high calories breakfast. There were 3 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

*Results*

One subject was withdrawn from the study due to being found with low neutrophil count and therefore meeting the predefined exclusion criteria. 17 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of sunitinib under fasted and fasting conditions.

| **Treatment N=17** | **$AUC_{0-72}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|
| **Test (fasting, T1)** | 1093.5 ± 346.3 | 30.1 ± 8.5 | 7.0 (6.0-12.0) |
| **Test (Fed, T2)** | 1119.4 ± 339.9 | 28.8 ± 7.4 | 12 (6.5-12.0) |
| **Reference (fasting, R)** | 1118.4 ± 348.3 | 31.5 ± 8.6 | 6.5 (6.0-12.0) |
| **Ratio (90% CI) T1:R** | 0.98<br>(0.94 -1.01) | 0.96<br>(0.90 -1.01) | -- |
| ***Ratio (90% CI) T1:T2** | 0.97<br>(0.94 -1.01) | 1.04<br>(0.98 -1.10) | -- |
| **Intra-subject variability** | 6.3% | 9.8% | -- |
| **$AUC_{0-72}$** area under the plasma concentration-time curve from time zero to 72 hours<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum concentration | | | |

**ln-transformed values*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for $AUC_{0-72}$ and $C_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Sunitinib Teva is considered bioequivalent with Sutent.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

### IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sunitinib Teva.

- Summary table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | - Hypertension<br>- Haemorrhagic events<br>- Cytopenic events<br>- Cardiotoxicity<br>o Torsade de pointes<br>o Left ventricular dysfunction/Heart Failure<br>o Pericardial events<br>o Cardiac ischemic events<br>- Fatigue and asthenia<br>- Thyroid dysfunction<br>- Serious infection<br>o Necrotising fasciitis<br>- Thrombotic microangiopathy<br>- Proteinuria/Nephrotic syndrome<br>- Reversible posterior leukoencephalopathy syndrome<br>- Fistula formation<br>- Hepatic failure<br>- Embolic and thrombotic/embolism and thrombosis<br>- Gastrointestinal perforation<br>- Pancreatitis<br>- Myopathy/Rhabdomyolysis<br>- Osteonecrosis of the jaw<br>- Oesophagitis<br>- Toxic epidermal necrolysis, Stevens-Johnson Syndrome, Erythema multiform<br>- Renal failure<br>- Adrenal gland dysfunction<br>- Cholecystitis<br>- Tumour lysis syndrome<br>- Angioedema<br>- Hypoglycaemia |
| Important potential risks | - Carcinogenicity<br>- Other potential cardiac effects:<br>o Conduction defect events<br>o Tachycardia events<br>- Retinal detachment<br>- Reproductive and developmental toxicity |
| Identified and potential interactions | - Drug interaction with CYP3A4 inhibitor or inducer |
| Missing information | - Use in paediatric patients<br>- Use in patients with severe hepatic impairment<br>- Use in patients with cardiac impairment |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sutent. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic

profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sunitinib Teva 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Sutent 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules. Sutent is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sunitinib Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 January 2018.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Procedure number | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
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