IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Temsirolimus Accord 30 mg concentrate and solvent for solution for infusion
Temsirolimus
PA2315/251/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA as RMS has granted a marketing authorisation for Temsirolimus Accord 30mg Concentrate and solvent for solution for infusion, from Accord Healthcare Limited on 25th June 2021: indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors.

This application is submitted under Directive 2001/83/EC, Article 10 (1) in cross-reference to the pharmaco-toxicological and clinical data supporting the European marketed formulation Torisel, marketed in Europe by Pfizer Ltd (EU/1/07/424/001).

The Applicant, Accord Healthcare Ltd, applies the marketing authorisation for Temsirolimus 30mg concentrate and solvent for solution for infusion through the Decentralised procedure, with IE as reference member state (RMS) and BE, BG, CZ, EE, ES, FR, HR, HU, PT, RO, SI as concerned member states (CMS).

Prescription status:
Many not be renewed (A)
Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie . *–to be completed if SmPC is in Nimbus*

Name of the product	Temsirolimus Accord 30mg Concentrate and solvent for solution for infusion
Name(s) of the active substance(s) (INN)	Temsirolimus
Pharmacotherapeutic classification (ATC code)	L01XE09
Pharmaceutical form and strength(s)	30mg Concentrate and solvent for solution for infusion
Marketing Authorisation Number(s) in Ireland (PA)	PA2315/251/001
Marketing Authorisation Holder	Accord Healthcare Limited
MRP/DCP No.	IE/H/562/001/DC
Reference Member State	IE
Concerned Member State	BE BG CZ EE ES FR HR HU PL RO SI

II. QUALITY ASPECTS

II.1. Introduction

This application is for Temsirolimus 30mg Concentrate and solvent for solution for infusion.

II.2 Drug substance

The active substance is Temsirolimus, an active substance and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each vial of concentrate for solution for infusion contains 30 mg temsirolimus.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with their corresponding Ph. Eur. monographs.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Parenteral preparations and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Temsirolimus 30mg Concentrate and solvent for solution for infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Torisel (Pfizer), on the European market. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of temsirolimus are well known. As temsirolimus is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Temsirolimus 30mg concentrate and solvent for solution for infusion 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.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of temsirolimus are well known. As temsirolimus is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

Temsirolimus is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Torisel marketed by MAH.

Temsirolimus is indicated for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors and for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

Temsirolimus 30mg concentrate and solvent for solution for infusion is a generic product to Torisel, claimed to share the same qualitative composition and to be essentially similar.

The pharmacodynamics and -kinetics of temsirolimus are well-known and the product is widely used with a well-known safety profile in the treatment of renal cell carcinoma.

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin), inhibiting the activity of mTOR that controls cell division. In addition to regulating cell cycle proteins, mTOR can regulate translation of the hypoxia-inducible factors, HIF-1 and HIF-2 alpha.

The applicant did not submit a bioequivalence study according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev.1), due to the fact that the medicinal product in the application is a concentrate and solvent for solution for infusion for intravenous use after reconstitution (initial dilution) and dilution (further dilution) and contains the same concentration of active substance (temsirolimus) in the same concentration as the currently authorized product i.e. Pfizer's Torisel® [Temsirolimus 30 mg concentrate and solvent for solution for infusion]. A biowaiver for bioequivalence studies was granted.

Please note that the initial SmPC was in accordance with the innovator's SmPC minus the therapeutic indication for mantle cell lymphoma. The applicant justified this omission due to a patent. However, despite this patent, given that all the safety data in relation to the MCL indication was being omitted from the labelling, it was subsequently requested (and agreed by the applicant) that the MCL indication would be re-instated in the common texts and to maintain the relevant safety data as per CMDh Q&A on usage patents: CMDh/279/2012, Rev. 1, May 2019 in the national texts.

A clinical overview dated 6th October 2017 with literature references were submitted. No new clinical studies were submitted.

IV.2 Pharmacokinetics

Absorption
Following administration of a single 25 mg intravenous dose of temsirolimus in patients with cancer, mean Cmax in whole blood was 585 ng/ml (coefficient of variation [CV] = 14%), and mean AUC in blood was 1627 ng•h/ml (CV = 26%). For patients receiving 175 mg weekly for 3 weeks followed by 75 mg weekly, estimated Cmax in whole blood at end of infusion was 2457 ng/ml during Week 1, and 2574 ng/ml during Week 3.

Distribution
Temsirolimus exhibits a polyexponential decline in whole blood concentrations, and distribution is attributable to preferential binding to FKBP-12 in blood cells. The mean ±standard deviation (SD) dissociation constant (Kd) of binding was 5.1 ± 3.0 ng/ml, denoting the concentration at which 50% of binding sites in blood cells were occupied. Temsirolimus distribution is dose-dependent with mean (10th, 90th percentiles) maximal specific binding in blood cells of 1.4 mg (0.47 to 2.5 mg). Following a single 25 mg temsirolimus intravenous dose, mean steady-state volume of distribution in whole blood of patients with cancer was 172 liters.

Biotransformation
Sirolimus, an equally potent metabolite to temsirolimus, was observed as the principal metabolite in humans following intravenous treatment. During in vitro temsirolimus metabolism studies, sirolimus, seco-temsirolimus and seco-sirolimus were observed; additional metabolic pathways were hydroxylation, reduction and demethylation. Following a single 25 mg intravenous dose in patients with cancer, sirolimus AUC was 2.7-fold that of temsirolimus AUC, due principally to the longer half-life of sirolimus.

Elimination
Following a single 25 mg intravenous dose of temsirolimus, temsirolimus mean ± SD systemic clearance from whole blood was 11.4 ± 2.4 l/h. Mean half-lives of temsirolimus and sirolimus were 17.7 hours and 73.3 hours, respectively. Following administration of [14C] temsirolimus, excretion was predominantly via the faeces (78%), with renal elimination of active substance and metabolites accounting for 4.6% of the administered dose. Sulfate or glucuronide conjugates were not detected in the human faecal samples, suggesting that sulfation and glucuronidation do not appear to be major pathways involved in the excretion of temsirolimus. Therefore, inhibitors of these metabolic pathways are not expected to affect the elimination of temsirolimus.

Model-predicted values for clearance from plasma, after applying a 175 mg dose for 3 weeks, and subsequently 75 mg for 3 weeks, indicate temsirolimus and sirolimus metabolite trough concentrations of approximately 1.2 ng/ml and 10.7 ng/ml, respectively.

Temsirolimus and sirolimus were demonstrated to be substrates for P-gp *in vitro*.

IV.3 Pharmacodynamics

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein/temsirolimus complex binds and inhibits the activity of mTOR that controls cell division. In vitro, at high concentrations (10-20 IM), temsirolimus can bind and inhibit mTOR in the absence of FKBP-12. Biphasic dose response of cell growth inhibition was observed. High concentrations resulted in complete cell growth inhibition in vitro, whereas inhibition mediated by FKBP-12/temsirolimus complex alone resulted in approximately 50% 16 decrease in cell proliferation. Inhibition of mTOR activity results in a G1 growth delay at nanomolar concentrations and growth arrest at micromolar concentrations in treated tumour cells resulting from selective disruption of translation of cell cycle regulatory proteins, such as D-type cyclins, c-myc, and ornithine decarboxylase. When mTOR activity is inhibited, its ability to phosphorylate, and thereby control the activity of protein translation factors (4E-BP1 and S6K, both downstream of mTOR in the P13 kinase/AKT pathway) that control cell division, is blocked.

In addition to regulating cell cycle proteins, mTOR can regulate translation of the hypoxia-inducible factors, HIF-1 and HIF-2 alpha. These transcription factors regulate the ability of tumours to adapt to hypoxic microenvironments and to produce the angiogenic factor vascular endothelial growth factor (VEGF). The anti-tumour effect of temsirolimus, therefore, may also in part stem from its ability to depress levels of HIF and VEGF in the tumour or tumour microenvironment, thereby impairing vessel development.

IV.4 Clinical Efficacy

The efficacy of temsirolimus is well characterised. No new clinical study was submitted. See Torisel EPAR for further details.

In advanced renal cell carcinoma, a main study involving 626 patients with poor prognosis found temsirolimus more effective than interferon alfa (another medicine used in the treatment of cancer) at prolonging patients' survival. Patients were treated with 25 mg temsirolimus, with interferon alfa or with 15 mg temsirolimus in combination with interferon alfa. Patients receiving temsirolimus alone survived 10.9 months on average compared with 7.3 months in those receiving interferon alfa alone. Patients receiving the lower dose of temsirolimus in combination with interferon alfa survived for a similar time (8.4 months) as those taking interferon alfa alone.

IV.5 Clinical Safety

The safety of temsirolimus is well characterised. No new clinical study was submitted. The safety of temsirolimus is well known with the reference medicinal product, Torisel authorised in 2007. See Torisel EPAR for further details.

The most common side effects with temsirolimus (which may affect more than 1 in 5 patients) include infections, pneumonia (infection of the lungs), thrombocytopenia (low blood platelet counts), anaemia (low red blood cell counts), decreased appetite, hyperglycaemia (high blood sugar levels), hypercholesterolaemia (high blood cholesterol levels), dysgeusia (taste disturbances), difficulty breathing, nose bleeds, cough, vomiting, stomatitis (inflammation of the lining of the mouth), diarrhoea, nausea (feeling sick), rash, pruritus (itching), oedema (swelling), tiredness, weakness, fever and mucosal inflammation (inflammation of moist body surfaces).

The most serious side effects of temsirolimus are allergic (hypersensitivity) reactions, serious reactions that occur during the infusion or soon afterwards, infections, lung disorders including pneumonitis (inflammation of the lungs) and pulmonary embolism (blood clot in the lung), bleeding in the brain, kidney failure, tearing (perforation) of the intestine, complications affecting the healing of wounds, hyperglycaemia (high blood sugar), thrombocytopenia (low levels of platelets), neutropenia (low levels of neutrophils, a type of white blood cell that fights infection) and hyperlipaemia (high blood levels of a type of fat).

For the full list of side effects, see the package leaflet.

Temsirolimus must not be used in people who are hypersensitive (allergic) to temsirolimus, to its metabolites (the substances that it is broken down into) including sirolimus (a medicine used to prevent rejection of transplanted kidneys), to polysorbate 80 or to any of the other ingredients of the medicine. Temsirolimus must not be used in patients with mantle cell lymphoma who have moderate or severe problems with their liver.

Risk Management Plan (RMP)

The applicant 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 temsirolimus concentrate and solvent for solution for infusion.
The RMP (version 1.2, dated 11/12/2020) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

The application contains an adequate review of published clinical data with an established safety & efficacy profile for the treatment of patients with renal cell carcinoma and mantle cell lymphoma. A biowaiver for bioequivalence studies was granted.

The benefit/risk is positive.

V. OVERALL CONCLUSIONS

Temsirolimus 30 mg concentrate and solvent for solution for infusion is a generic form of Torisel. Torisel is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence was not required due to the intravenous formulation in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Temsirolimus 30 mg concentrate and solvent for solution for infusion demonstrated a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

07.02.2026