Date: 10 November 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tavneos

International non-proprietary name: avacopan
Pharmaceutical form: hard capsule
Dosage strength(s): 10 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Vifor Fresenius Medical Care
Marketing Authorisation No.: 66772
Decision and Decision date: approved on 19 September 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
ANCA	Anti-neutrophil cytoplasmic autoantibody
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
C5aR1	C5a receptor
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
GPA	Granulomatosis with polyangiitis
hERG	Human ether-à-go-go-related gene
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
M1	Major human metabolite
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MPA	Microscopic polyangiitis
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
rh	Relative humidity
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance avacopan of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan Drug Status was granted on 20 September 2017.

Work-sharing procedure
The applicant requested a work-sharing procedure with Canada and Switzerland.
The Access NAS (New Active Substance) work-sharing initiative is a collaboration between regulatory authorities, i.e. Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA), Swissmedic and the pharmaceutical industry.
The work-sharing initiative coordinates the assessment of a NAS application that has been filed in at least two jurisdictions.

2.2 Indication and Dosage

2.2.1 Requested Indication

Avacopan is indicated for the treatment of adult patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis (Wegener's) [GPA] or microscopic polyangiitis [MPA]).

2.2.2 Approved Indication

Tavneos, as an adjunctive treatment to standard immunosuppressive treatment that includes rituximab or cyclophosphamide with glucocorticoids, is indicated for the treatment of adult patients with severe, active antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)).

2.2.3 Requested Dosage

Summary of the requested standard dosage:
Treatment with Tavneos should be initiated and monitored by healthcare professionals experienced in the diagnosis and treatment of granulomatosis with polyangiitis and microscopic polyangiitis.

The recommended dose of Tavneos is 30 mg (3 hard capsules of 10 mg each) taken orally twice daily, morning and evening, with food.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	12 April 2021
Formal control completed	25 May 2021
List of Questions (LoQ)	21 September 2021
Answers to LoQ	4 November 2021
Preliminary decision	18 February 2022
Answers to Preliminary decision	3 March 2022
Labelling corrections	1 July 2022
Answers to Labelling corrections	28 July 2022
Final Decision	19 September 2022
Decision	approval

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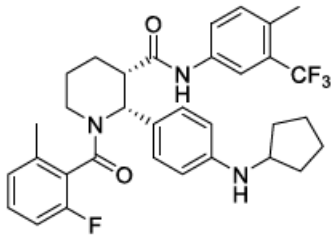
3 Quality Aspects

3.1 Drug Substance

INN: Avacopan
Chemical name: (2*R*,3*S*)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-*N*-[4methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide
Molecular formula: $C_{33}H_{35}F_4N_3O_2$
Molecular mass: 581.6435 Da
Molecular structure:



Physico-chemical properties:
Avacopan is a white to pale yellow crystalline solid. The compound contains two chirality centres and is manufactured as a single stereoisomer. It is practically insoluble in water and is non-hygroscopic. Avacopan exhibits polymorphism.

Synthesis:
The synthesis of avacopan consists of several chemical transformation steps. Adequate information is provided regarding the manufacturing process, materials, critical steps and intermediates.

Specification:
The drug substance specification includes tests for appearance, identification, assay, impurities, residual solvents, elemental impurities, water content and residue on ignition. The applied limits are justified and in line with the relevant guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability:
The stability of the drug substance was investigated with commercial scale batches which were manufactured by the proposed commercial manufacturing site. The stability samples were stored under long-term conditions (25°C/60% rh) and accelerated conditions (40°C/75% rh) as defined in the corresponding ICH Guideline on stability studies. Based on these studies, an adequate retest period was defined.

3.2 Drug Product

Swissmedic has not assessed the primary data relating to the Drug Product of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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4 Nonclinical Aspects

4.1 Pharmacology

Avacopan inhibited the C5a receptor (C5aR1) *in vitro* at concentrations in the range of the clinical concentration range (0.4-0.6 nM, unbound). The antagonistic activity was assessed through Ca5 binding, Ca5-mediated calcium mobilisation, chemotaxis and CD11b upregulation in human granulocytes. Activity on cynomolgus monkey and hamster C5aR1 was in the nanomolar range as well. The major human metabolite M1 had a similar potency. Avacopan had no or low pharmacological activity on mouse, rat and rabbit C5aR1 in concentrations up to 4 or 10 µM.
In a human C5aR knock-in mouse model, avacopan blocked C5a-mediated leukopenia with an IC_{50} of 15 nM and *ex vivo* CD11b upregulation in neutrophils with an IC_{50} of 4.75 nM. Similarly, avacopan inhibited C5a-induced neutropenia in cynomolgus monkeys at clinically relevant exposures. Also, the drug substantially reduced the percentage of glomeruli with crescents and necrosis at clinically relevant exposures in an ANCA-vasculitis mouse model.
Secondary pharmacology studies demonstrated that avacopan is a highly selective antagonist of C5aR1 without any relevant off-target activity at the clinical exposure.
Safety pharmacology studies in rats and the in vitro hERG assay did not indicate any alert at the clinical exposure. It is noted that avacopan is not pharmacologically active in rats. However, additional assessments of behaviour, electrocardiogram, respiratory and renal function in the monkey toxicity studies at exposures in excess of the clinical exposure did not raise safety concerns.

4.2 Pharmacokinetics

Avacopan has low solubility and high permeability *in vitro*. Total body clearance was moderate following IV administration (30-50% of liver blood flow).To improve oral bioavailability an optimised oral formulation was used for the toxicology study which was not identical to the clinical formulation. After oral administration of the improved formulation avacopan was rapidly absorbed with a T_{max} of 1-2 h in rodents and 3.3-4 h in monkeys. Oral bioavailability was moderate to high (87% in mice and 55-104% in rats). Elimination half-lives were 2.9-5.6h in rodents and 6-15.3 h in monkeys. Exposures reached a plateau at approximately 100 mg/kg in rats and rabbits and 50 mg/kg in monkeys after short-term dosing. Exposure to avacopan and M1 was higher after repeated long-term dosing and increased less than dose proportionally at doses ≥ 15 mg/kg/day for avacopan. There were no gender-related differences in exposure.
Avacopan bound strongly to plasma proteins in all animal species and in humans (>99.9%) *in vitro*. There was no preferential partitioning to red blood cells. Avacopan-related radioactivity rapidly distributed to most tissues and organs in rats following single oral administration of 15 mg/kg. There was low distribution into the brain and spinal cord. Avacopan bound melanin-containing tissues in the eyes of pigmented rats. After 14 days, radioactivity was still detectable in various tissues. Placental transfer and the excretion into milk of avacopan were not assessed.
All metabolites that were detected *in vitro* in human microsomes and hepatocytes were also found in at least one animal species used in the toxicology studies (rat, hamster, rabbit, monkey) and were mainly Phase I products. The avacopan plasma content was 50-65% of total radioactivity in rats, 12% in monkeys and 30-50% in humans. The only major circulating human metabolite M1, a methyl hydroxylation product (~12% of the total drug-related material), was also formed in the animal species. CYP3A4 was found to be the main enzyme for metabolism of avacopan. Elimination half-lives of total radioactivity were >88 h in rats, 144 h in monkeys and up to 21 days (510 h) in humans. Excretion was mainly via the faecal/biliary route in the animal species and humans.

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4.3 Toxicology

All animal species (rat, hamster, rabbit and cynomolgus monkey) were considered suitable based on their ADME profile, while hamster and cynomolgus monkey were also pharmacologically relevant. The dosing scheme (twice daily) and studies up to 13 weeks in hamsters, 26 weeks in rats and 44 weeks (including 5 weeks of nasogastric administration) in monkeys with oral administration, support the clinical dosing scheme for chronic treatment. Exposure of M1 was covered in the studies.
No adverse effects of avacopan were observed in the repeat-dose toxicity studies up to the highest dose levels, corresponding to safety margins of 13.9 in rats, 4.7 in hamsters and 4.3 in monkeys. It is acknowledged that the animal exposure could not be further increased substantially despite efforts to optimise the dose formulation or use of a different dosing route (oral and nasogastric administration in monkeys).
Avacopan was not genotoxic in a standard genotoxicity testing battery.
Two-year carcinogenicity studies in rats and hamsters did not indicate any tumorigenic potential at exposures 3.7- to 6-fold the clinical exposure for avacopan and at the clinical exposure for M1.
Fertility of hamsters was not affected at exposures 6.8-fold the clinical AUC. Embryofetal development studies were conducted in hamsters and rabbits. There were no fetal findings except for short thoracolumbar supernumerary ribs (skeletal variation) in the hamster at an exposure 5.3-fold the clinical AUC. There was an increased incidence of abortions compared to control groups in rabbits. The applicant considered this only relevant at the highest dose level. As there was a <2-fold difference in exposure across the avacopan dose groups, a NOAEL for maternal toxicity is considered to be not established in rabbits. Exposure at the highest dose, i.e. the embryofetal NOAEL, was below the clinical exposure.
There were no adverse findings in the pre- and postnatal development study in hamsters up to an exposure 6.3-fold the clinical exposure.
Avacopan should not be given during pregnancy and lactation according to the Information for healthcare professionals.
Avacopan had no phototoxic potential *in vitro*.
It is noted that the T cell-dependent antibody response (TDAR) assessments in the 13-week rat study and in the 44-week monkey study had some technical limitations. As the rat is not considered to be a pharmacologically relevant species, target-related immunotoxicity could not be appropriately assessed. However, the overall toxicity profile in monkeys and hamsters did not indicate an immunotoxicity risk.
There are no concerns with regard to the impurities or excipients.
Based on the ERA, the risk for the environment resulting from use of avacopan is considered to be low.
According to the PIP, two studies in juvenile animals are still pending.

The RMP provides adequate information about the nonclinical data.

4.4 Nonclinical Conclusions

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Tavneos with the active ingredient avacopan in the proposed indication. The pharmacological properties and the pharmacokinetic and toxicity profiles of avacopan were adequately characterised. There are no concerns from the nonclinical standpoint regarding approval. All nonclinical data that are relevant for safety are included in the Information for healthcare professionals.

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5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's Request / Work-sharing procedure).

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Tavneos, hard capsules was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

TAVNEOS®

Composition

Active substances

Avacopan

Excipients

Hard capsule content
Macrogolglycerol Hydroxystearate (245 mg/capsule)
Macrogol (4000)

Hard capsule shell
Gelatin
Red iron oxide (E172)
Yellow iron oxide (E172)
Black iron oxide (E172)
Titanium dioxide (E171)
Polysorbate 80

Pharmaceutical form and active substance quantity per unit

Hard capsule

Appearance
Hard capsules are made of a yellow body and light orange cap with “CCX168” in black ink.
Hard capsules have a length of 22 mm and a diameter of 8 mm.

Amount of active ingredient per unit
Each hard capsule contains 10 mg of avacopan.

Indications/Uses

Tavneos, as an adjunctive treatment to standard immunosuppressive treatment that includes rituximab or cyclophosphamide with glucocorticoids, is indicated for the treatment of adult patients with severe, active antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)).

Dosage/Administration

Treatment with Tavneos must be initiated and monitored by healthcare professionals with experience in the diagnosis and treatment of ANCA-associated vasculitis (GPA and MPA).

Dose adjustment/titration

The recommended dose of Tavneos is 30 mg (3 hard capsules of 10 mg each) taken orally twice daily, in the morning and evening, with food.

Rituximab or cyclophosphamide with glucocorticoids should be administered as follows:

- rituximab for 4 weekly intravenous doses, or,
- intravenous or oral cyclophosphamide for 13 or 14 weeks, followed by oral azathioprine or mycophenolate mofetil and
- glucocorticoids, as clinically indicated.

Initiation of treatment

Before starting Tavneos, consider the following tests:

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and hepatitis B virus (HBV) serology should be performed prior to initiating Tavneos therapy to assess baseline liver function.

A physician specialised in the management of hepatitis B must be consulted regarding patients with evidence of previous or current HBV infection to assess the need for HBV treatment prior to or during treatment with Tavneos.

The use of Tavneos is not recommended in patients with cirrhosis, particularly in patients with severe hepatic impairment (Child-Pugh class C) (see Special warnings and precautions for use, Hepatotoxicity).

Dosage adjustment following undesirable effects/interactions

Treatment must be clinically re-assessed and temporarily discontinued if:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels are higher than 3 times the upper limit of normal (ULN) and less than 5 times the ULN.

Tavneos treatment must be stopped temporarily if:

- ALT or AST is greater than 5 times the ULN.
- The patient shows leukopenia (white blood cell count < 2×10^9/L) or neutropenia (neutrophil count < 1×10^9/L), or lymphopenia (lymphocyte count < 0.2×10^9/L).
- The patient has an active and serious infection.

Treatment with Tavneos can be resumed:

- Once the possibility of drug-induced liver injury has been ruled out.
- After normalisation of liver function parameters based on an individual benefit/risk assessment.

If treatment is resumed, transaminases and total bilirubin levels must be closely monitored.

Permanent discontinuation of the treatment must be considered in any of the following situations:

- ALT or AST >8 times the ULN;
- ALT or AST >5 times the ULN for more than 2 weeks;
- ALT or AST level >3 times the ULN and total bilirubin level >2 times the ULN or INR (International Normalised Ratio) >1.5;
- ALT or AST >3 times the ULN with fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, with fever, rash and/or eosinophilia (>5%);
- An association between Tavneos and liver dysfunction has been established.

Patients with hepatic disorders

No dosage adjustment is required for patients with mild to moderate hepatic impairment (as indicated by Child-Pugh).
Tavneos has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and therefore is not recommended for use in these patient populations.

Patients with renal disorders

No dosage adjustment is required in patients with mild, moderate or severe renal function impairment.
Tavneos has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

Elderly patients

Of the 86 elderly patients who received Tavneos in the randomised Phase III clinical trial in ANCA-associated vasculitis, 62 patients were 65-74 years old and 24 patients were 75 years old or older. No differences in overall safety or efficacy were observed between elderly and younger patients.
No dose adjustment is required in elderly patients.

Children and adolescents

The safety and efficacy of Tavneos in children (under 18 years of age) have not yet been established. Data in adolescents (aged 12-17 years) are limited. There is no information available for children under 12 years of age. Based on the limited information, no recommendation on final dosing for children aged 12 to 17 years can be given.

Delayed administration

If a patient misses a dose, the missed dose is to be taken as soon as possible, unless within three hours of the next scheduled dose. If within three hours of the next scheduled dose, the missed dose is not to be taken and the next dose be taken normally. Inform the patient not to double the next dose.

Mode of administration

Tavneos is intended for oral use.
The hard capsules must be swallowed whole with water during a meal and must not be crushed, chewed or opened.
Grapefruit juice is to be avoided in patients treated with Tavneos.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Hepatotoxicity

Serious hepatic injury has been observed in patients receiving Tavneos. Clinical trials have reported an increased incidence of transaminase elevations and hepatobiliary events in patients treated with Tavneos, including severe and life-threatening cases (see Adverse Reactions).

Liver function tests (serum alanine aminotransferase [ALT], serum aspartate aminotransferase [AST], alkaline phosphatase and total bilirubin) must be performed before initiating Tavneos, every 4 weeks after therapy initiation for the first 6 months, and as often as clinically indicated thereafter. Patients must be monitored for liver transaminases and total bilirubin if clinically indicated and as part of the routine monitoring of the patient's underlying disease.

Tavneos must be avoided in patients with signs of liver disease, such as elevated AST, ALT, alkaline phosphatase (ALP) or total bilirubin higher than 3 times the ULN.

Tavneos is not recommended for use in patients with chronic, active, untreated and/or uncontrolled liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) or cirrhosis. It is important to consider the risks and benefits of the drug before administering it to a patient with liver disease. Patients must be closely monitored for the development of hepatic adverse reactions.

Angioedema

Tavneos may cause angioedema (see Adverse Reactions). In clinical trials, two cases of angioedema were reported, one of which was severe and required hospitalisation. In case of angioedema, Tavneos must be discontinued immediately and appropriate care and monitoring for impairment of the respiratory tract must be undertaken. Tavneos must not be resumed unless another cause has been identified. Patients should be trained to recognise the signs and symptoms of a hypersensitivity reaction and should seek immediate medical care if one occurs.

Blood and Immune System

A white blood cell count must be performed before initiating treatment and patients must be monitored as clinically indicated, as part of routine follow-ups of the patient's underlying condition.

Treatment with Tavneos must not be initiated if the white blood cell count is less than 3,500/μL, the neutrophil count less than 1,500/μL, or the lymphocyte count less than 500/μL.

Patients receiving Tavneos must immediately report any signs of infection, unexpected bruising, bleeding, or other manifestations of bone marrow failure.

Serious Infections

Serious infections, including fatal cases, have been reported in patients treated with Tavneos. The most frequently reported serious infections in the Tavneos group were pneumonia (4.8%) and urinary tract infections (1.8%).

Tavneos must not be administered to patients with active and severe infections, including localised infections. The risks and benefits must be considered before initiating treatment with Tavneos in patients:

- with a chronic or recurrent infection;
- with a history of tuberculosis;
- with a history of severe or opportunistic infections;
- who have visited or travelled to areas with endemic tuberculosis or fungal infections; or
- who have underlying conditions that may predispose them to infections.

During and after treatment with Tavneos, patients must be closely monitored for signs and symptoms of infection.

Tavneos must be discontinued in the event of a serious or opportunistic infection. Perform a prompt and complete diagnostic test adapted to immunosuppression, if a patient develops a new infection during treatment with Tavneos. Appropriate antimicrobial therapy should be started, and the patient closely monitored. Tavneos should be stopped if the patient does not respond to this treatment. Tavneos treatment can continue only after the infection is under control.

Prophylactic treatment of *Pneumocystis jirovecii* pneumonia

Administration of prophylactic treatment for *Pneumocystis jirovecii* pneumonia is recommended during treatment with Tavneos in adult patients with GPA or MPA, in accordance with local clinical practice guidelines.

Reactivation of the Hepatitis B virus

Hepatitis B virus (HBV) reactivation, including life-threatening hepatitis B, has been observed in the clinical program.

HBV reactivation is defined as an abrupt increase in HBV replication, which manifests through an increase in serum HBV DNA levels or HBsAg detection in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e. increased levels of transaminases. In severe cases, increased bilirubin levels, liver failure, and death may occur.

Patients must be screened for HBV infection by measuring HBsAg and anti-HBc before starting treatment with Tavneos.

Patients with evidence of past or current hepatitis B virus (HBV) infection must be seen by a physician specialised in the management of hepatitis B for monitoring and possible HBV infection treatment before and/or during treatment with Tavneos.

Patients showing signs of current or previous HBV infection based on clinical and laboratory examinations that may indicate signs of hepatitis or HBV reactivation must be monitored for six months following treatment with Tavneos.

In patients who develop HBV reactivation while on Tavneos, immediately discontinue Tavneos and any concomitant therapies associated with HBV reactivation and start appropriate treatment. There is insufficient data on the safety of resuming Tavneos in patients who have developed HBV reactivation.

Resumption of treatment with Tavneos in patients whose HBV reactivation has resolved should be discussed with physicians specialised in the management of HBV infection.

Cardiac disorders

Patients with GPA or MPA are at risk of cardiac disorders such as myocardial infarction, cardiac failure, and cardiac vasculitis. Serious adverse events (SAEs) of cardiac disorder have been reported in patients treated with Tavneos. Some treatment regimens may increase the risk of cardiac disorders (a regimen based on a combination of cyclophosphamide followed by azathioprine may carry an increased risk of cardiac disorders, as compared to a regimen based on the combination with rituximab).

Immunisation

The safety of immunisation with live vaccines after taking Tavneos has not been studied. Vaccines should preferably be administered before starting treatment with Tavneos or during the remission phase of the disease.

Malignancy

Immunomodulatory medicinal products may increase the risk of malignancies. Clinical data is currently limited.

Interaction with strong CYP3A4 inducers

The use of strong CYP3A4 enzyme inducers (e.g., carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifampicin, and St. John's Wort) with Tavneos is to be avoided (see Interactions). Patients anticipated to require long-term administration of these medicinal products are not to be treated with Tavneos. If short-term co-administration cannot be avoided in a patient already using Tavneos, the patient must be closely monitored for any reoccurrence of disease activity.

Macrogolglycerol Hydroxystearate

Tavneos contains macrogolglycerol hydroxystearate as an excipient, which may upset the stomach and cause diarrhoea.

Interactions

Avacopan is a substrate of CYP3A4. Concomitant administration of inducers or inhibitors of this enzyme may affect the pharmacokinetics of avacopan.

Influence of other substances on the pharmacokinetics of avacopan

Effect of strong CYP3A4 inducers on avacopan

Co-administration of avacopan and rifampicin, a potent inducer of CYP3A4, resulted in a decrease in the area under the concentration-time curve (AUC) and the maximum concentration (C_{max}) of avacopan in plasma by approximately 93% (geometric mean ratio [GMR]: 7%) and 79% (GMR: 21%), respectively. As this interaction may result in loss of avacopan efficacy, the use of strong inducers of CYP3A4 (e.g., carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifampicin and St. John's wort) with avacopan is to be avoided. Patients who are scheduled for long-term administration of these medicinal products are not to be treated with avacopan. If short-term co-administration cannot be avoided in a patient already receiving avacopan, the patient should be closely monitored for any reoccurrence of disease activity.

Effect of moderate CYP3A4 inducers on avacopan

Concomitant administration of moderate inducers (e.g., bosentan, efavirenz, etravirine and modafinil) is not recommended. If concomitant administration cannot be avoided in a patient already using avacopan, there should be close monitoring for reoccurrence of disease activity.

Effect of potent CYP3A4 inhibitors on avacopan

Co-administration of avacopan with itraconazole, a potent CYP3A4 inhibitor, resulted in an increase in avacopan AUC and C_{max} of approximately 119% (GMR: 219%) and 87% (GMR: 187%), respectively. Therefore, the dose of avacopan should be reduced to 30 mg once daily when strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) are co-administered with avacopan.

Grapefruit and grapefruit juice can increase avacopan concentration; therefore, grapefruit and grapefruit juice are to be avoided in patients treated with avacopan.

Influence of avacopan on the pharmacokinetics of other medicinal products

Effect of avacopan on substrates of cytochrome P450 (CYP) 3A4 and 2C9

Avacopan is a weak inhibitor of CYP3A4 and CYP2C9, as indicated by a modest increase in the AUC of drugs tested such as midazolam (1.81 times) and celecoxib (1.15 times), respectively.

Avacopan may increase the plasma levels of concomitant drugs that are substrates of CYP3A4 or CYP2C9.

Be cautious when CYP3A4 substrates with a narrow therapeutic index (e.g., alfentanil, ciclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) are used with avacopan. Patients should be managed in accordance with the professional information of medicinal products with a narrow therapeutic index.

Effect of avacopan on substrates of other cytochromes P450 (CYP)

In vitro, avacopan is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6, nor an inducer of CYP1A2 and CYP2B6. Therefore, when avacopan is co-

administered with substrates of these CYP enzymes, it is unlikely to significantly affect the exposure of substances that are metabolised by these CYP enzymes.

Effect of avacopan on transporters

Avacopan showed negligible to weak inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K *in vitro*.

Effect of macrogolglycerol hydroxystearate on sensitive P-glycoprotein (P-gp) substrates.
A clinically relevant effect of the excipient macrogolglycerol hydroxystearate on sensitive P-gp substrates with relatively low bioavailability (e.g., dabigatran etexilate) cannot be excluded. Exercise caution when using low-bioavailability P-gp substrates in patients who are being treated with avacopan.

Pregnancy, lactation

Pregnancy

There is no data on the use of avacopan in pregnant women.
Animal studies have shown evidence of reproductive toxicity (see Preclinical safety data).
Avacopan is not recommended during pregnancy and in women of childbearing potential not using contraception.
Women of childbearing potential must use effective contraception during treatment and for 3 months after treatment discontinuation.

Lactation

In animals, avacopan was not measured in the milk of lactating females; however, avacopan was detected in the plasma of nursing animal offspring with no apparent effects on the offspring. There is no data in nursing women. It is not known if avacopan is excreted through breast milk. A risk to neonates/infants cannot be excluded. A decision must be taken whether to discontinue breastfeeding or avacopan considering the benefit of breastfeeding for the child compared to the benefit of the treatment for the woman.

Fertility

There is no data on the effects of avacopan on human fertility. Animal data did not indicate any impairment of male or female fertility.

Effects on ability to drive and use machines

Tavneos has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The safety of Tavneos was evaluated in two (2) phase II clinical studies and one (1) phase III clinical study with a total of 239 subjects with ANCA-associated vasculitis who received at least one dose of Tavneos.

Adverse reactions were determined based on data coming from the Tavneos clinical development program. The frequencies of adverse drug reactions (ADRs) are those reported in the pivotal phase III study (n=330); of these 330 subjects, 166 were in the Tavneos group and 164 were in the prednisone group.

The most common adverse drug reactions in patients with ANCA-associated vasculitis who received Tavneos in combination with cyclophosphamide or azathioprine or mycophenolate mofetil or rituximab were headache (20.5%), nausea (23.5%) and vomiting (15.1%).

Only one treatment emergent adverse event (TEAE) of nausea was considered serious. There were no reports of vomiting and headache that were considered serious. The serious adverse reactions that were reported more frequently in the Tavneos-treated patients than in the prednisone groups were pneumonia (4.8% vs. 3.7%), urinary tract infection (1.8% vs. 1.2%) and liver function abnormality (1.2% vs. 0.0%).

In the pivotal phase III study, 7 patients (4.2%) in the Tavneos group and 2 patients (1.2%) in the prednisone group discontinued treatment due to hepatic adverse reactions, including hepatobiliary adverse events and liver enzyme abnormalities. The most common adverse reaction that lead to discontinuation in at least 1 patient was liver function abnormalities (1.8%), which was more common in patients treated with Tavneos.

In the pivotal phase III study, 2 subjects (1.2%) in the Tavneos group experienced an angioedema TEAE. One subject was hospitalised due to this event. Tavneos treatment was discontinued, and the angioedema did not reappear.

List of adverse reactions

The adverse reactions observed in the ANCA-associated vasculitis pivotal phase 3 study in patients treated with Tavneos are listed in Table 1 by system organ class (SOC) and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100). Within each frequency group, adverse reactions are presented in the order of decreasing seriousness.

Table1: Summary of adverse reactions in the pivotal phase III ANCA-associated vasculitis study.

Organ system	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**
Infections and infestations	Upper respiratory tract infection, Nasopharyngitis	Pneumonia, Lower respiratory tract infection, Influenza, Bronchitis, Cellulitis, Urinary tract infections Shingles, Sinusitis, Oral candidiasis, Oral herpes, Middle ear infection, Rhinitis, Gastroenteritis	
Blood and lymphatic system disorders		Neutropenia	
Nervous system disorders	Headache		
Gastrointestinal disorders	Vomiting Diarrhoea Nausea	Upper abdominal pain	
Hepatobiliary disorders	Increased liver test results*		
Skin and subcutaneous tissue disorders			Angioedemas
Investigations			
	Decreased white blood cell count**	Increased creatine phosphokinase in blood	

*Increased alanine aminotransferase, increased total blood bilirubin, abnormal liver function, increased gamma-glutamyl transferase, increased liver enzyme, increased transaminases.
**Including leukopenia

Description of specific adverse reactions and additional information

Hepatotoxicity and increased liver function test results

In the pivotal phase III study, which involved the treatment of 330 patients, a total of 19 patients (11.6%) in the prednisone group and 22 patients (13.3%) in the Tavneos group experienced hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzyme abnormalities. The study drug was discontinued or permanently stopped due to liver enzyme abnormalities in 5 patients (3.0%) in the prednisone group and 9 patients (5.4%) in the Tavneos group. Serious hepatic adverse reactions were reported in 6 patients (3.7%) in the prednisone group and in 9 patients (5.4%) in the Tavneos group. One serious hepatic adverse reaction was reported in one patient in the Tavneos group in the phase II studies.

Increased creatine phosphokinase

In the pivotal phase III study, 1 patient (0.6%) in the prednisone group and 6 patients (3.6%) in the Tavneos group experienced adverse reactions of increased creatine phosphokinase (CPK). One patient treated with Tavneos discontinued treatment due to increased creatine phosphokinase.

Hypersensitivity, including angioedema

In the pivotal phase III study, 2 patients (1.2%) in the Tavneos group experienced an adverse event of angioedema. One patient was hospitalised due to this event. Tavneos was discontinued and both events resolved without sequelae. Tavneos was resumed in one patient and the angioedema did not reappear.

Paediatric population

Due to limited data in adolescents (12-17 years of age), the safety and efficacy of Tavneos in adolescents has not been established yet. There is no data in children under 12 years of age.

Specific populations

Elderly population
In clinical studies, the safety profile was identical in patients of 65 years old or more and in adults less than 65 years old.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are required to report any suspected new or serious adverse reactions via the online reporting portal ElViS (Electronic Vigilance System). For more information about this, visit www.swissmedic.ch.

Overdose

Tavneos has been studied in healthy subjects at a maximum total daily dose of 200 mg (administered as a 100 mg dose twice daily) for 7 days without evidence of dose-limiting toxicity. In the event of an overdose, it is recommended to monitor the patient for signs and symptoms of adverse reactions and that appropriate symptomatic treatment and supportive care are provided.

Properties/Effects

ATC code: not yet assigned

Mechanism of action

Avacopan is a selective antagonist of the human complement component 5a receptor (C5aR1 or CD88) that competitively inhibits the interaction between C5aR1 and the anaphylatoxin C5a. C5a and C5aR1 play a central role in the pathogenesis of ANCA-associated vasculitis. Specific and selective blockade of C5aR1 by avacopan reduces the pro-inflammatory effects of C5a, which include neutrophil activation and migration, and leads to decreased adhesion at inflammation sites in small blood vessels, vascular endothelial cell retraction and increased permeability.

Pharmacodynamics

Avacopan blocks C5a-induced activation of CD11b (integrin alpha M) on neutrophils collected from humans receiving avacopan. CD11b facilitates neutrophil adherence to vascular endothelial surfaces, one of the steps in the vasculitis process.

Cardiac electrophysiology

At the recommended authorised dose, avacopan does not prolong the QT interval in a clinically meaningful way.

Clinical efficacy

A total of 330 patients aged 13 years or older with polyangiitis granulomatosis (GPA) (54.8%) or microscopic polyangiitis (MPA) (45.2%) were treated in the randomised, multicentre, active comparator, double-dummy, double-blind, 52-week, pivotal phase III ADVOCATE study.

Patients were randomised in a 1 to 1 ratio to one of two groups:

- Avacopan group (N=166): Patients received avacopan 30 mg twice daily for 52 weeks plus prednisone-matching placebo tapering regimen over 20 weeks,
- Prednisone group (N=164): Patients received an avacopan placebo twice daily for 52 weeks plus prednisone (tapered from 60 mg/day to 0 over 20 weeks).

All patients in both groups received standard immunosuppressive regimens of either:

- Rituximab 375 mg/m² in 4 weekly intravenous doses, or
- Cyclophosphamide intravenously for 13 weeks (15 mg/kg up to 1.2 g every 2-3 weeks), and then from week 15 onwards, azathioprine orally 1 mg/kg per day, with titration up to 2 mg/kg per day (mycophenolate mofetil 2 g per day was allowed instead of azathioprine. If mycophenolate mofetil was not tolerated or not available, enteric-coated mycophenolate sodium could be given at a target dose of 1,440 mg/day), or
- Cyclophosphamide orally for 14 weeks (2 mg/kg per day) followed by oral azathioprine or mycophenolate, mofetil/sodium from week 15 onwards (same dosing schedule as intravenous cyclophosphamide doses).

Dose reductions or adjustments of cyclophosphamide, azathioprine and mycophenolate were permitted in accordance with standard practice to maximise the safety of these drugs.

Glucocorticoids were allowed as pre-medication for rituximab to reduce hypersensitivity reactions, to taper glucocorticoids administered during the screening period, to treat persistent vasculitis, worsening of vasculitis or relapses, and for non-vasculitis related reasons such as adrenal insufficiency.

Patients were stratified at time of randomisation to obtain a balance between treatment groups according to 3 factors:

- Newly diagnosed or relapsed ANCA-associated vasculitis.
- ANCA-associated vasculitis positive for myeloperoxidase (MPO) or proteinase 3 (PR3).
- Treated with either intravenous rituximab or intravenous or oral cyclophosphamide.

The primary objective was to evaluate the efficacy of the above-described treatment regimens to induce and sustain remission in patients with ANCA-associated vasculitis based on the following two primary endpoints:

- the proportion of patients in disease remission defined as achieving a Birmingham Vasculitis Activity Score (BVAS) of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to week 26,
- the proportion of patients in sustained remission defined as remission at week 26 without relapse to week 52, and BVAS of 0 and not taking glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to week 52.

The initial demographic and pathological profiles of the patients were balanced between the two treatment groups. The mean age of the patients was 60.9 years. Most patients were male (56.4%), Caucasian (84.2%) and had been newly diagnosed with the disease (69.4%). Patients had either GPA (54.8%) or MPA (45.2%) and had anti-PR3 antibodies (43.0%) or anti-MPO (57.0%) antibodies. The mean initial BVAS score was 16.2; patients most frequently had renal (81.2%), general (68.2%), ENT (43.6%) and chest (43.0%) manifestations. Approximately 65% of patients received rituximab, 31% received i.v. cyclophosphamide and 4% received oral cyclophosphamide.

Remission at Week 26 and sustained remission at Week 52
72.3% of patients in the TAVNEOS arm and 70.1% of patients in the prednisone arm achieved remission at week 26 (difference between treatments: 3.4%, 95% CI [-6.0%, 12.8%]). At week 52, a significantly higher percentage of patients had achieved sustained remission in the TAVNEOS group (65.7%) compared to the prednisone group (54.9%) (difference between treatments: 12.5%, 95% CI [2.6%, 22.3%]; P = 0.0066).

Glucocorticoids
Tavneos does not eliminate the use of Glucocorticoids. In the phase 3 trial, the mean total cumulative prednisone-equivalent dose from day 1 to end-of-treatment was 3,654.5mg in the comparator group and 1,348.9mg in the avacopan group. In the comparator group, the majority of glucocorticoids use was due to the protocol-defined prednisolone course.

Pharmacokinetics

Absorption

When administered without food, avacopan peak plasma concentration (C_{max}) occurs at a median time (t_{max}) of approximately 2 hours. Based on population pharmacokinetic analysis, the estimated mean plasma exposure of avacopan and the M1 metabolite at steady state are 3,466

± 1,921 ng-h/ml and 1,283 ± 541 ng-h/ml, respectively for the area under the 12-hour plasma drug concentration curve (AUC_{0-12h}) and 349 ± 169 ng-h/ml, 122 ± 49.4 ng-h/ml, respectively, for the maximum plasma concentration (C_{max}) in patients with ANCA-associated vasculitis receiving avacopan 30 mg twice daily. Steady-state plasma concentrations of avacopan are reached within 13 weeks and accumulation is approximately 4-fold.
Avacopan showed an approximate dose-proportional increase in systemic exposure over the dose ranging from 10 to 100 mg. The absorption fraction in humans is at least 93% in a solution formulation.

Co-administration of a 30 mg hard capsule and a high-fat, high-calorie meal increases the plasma exposure (AUC) of avacopan by approximately 72% (AUC ratio food/fasting = 1.72) and delays the t_{max} by approximately 3 hours. However, it has no effect on C_{max}. Eating had no observable significant effect on the M1 metabolite AUC, but its C_{max} was 51% lower in the fed state.

Distribution

The reversible plasma protein binding (e.g. to albumin and alpha-1-acid glycoprotein) of avacopan and the M1 metabolite is greater than 99.9%. The apparent volume of distribution is high (Vz/F 3,000-11,000 L), indicating broad tissue distribution of the drug.

Metabolism

Avacopan is eliminated mainly through phase I metabolism. Following oral administration of radiolabelled avacopan, the bulk of the active substance-related materials was recovered in the faeces as phase I metabolites. A major circulating metabolite (M1), a monohydroxylated product of avacopan, was present in ~12% of the total active substance-related materials in plasma. This metabolite constitutes 30-50% of the parent exposure and has approximately the same effect on C5aR1 as avacopan. Cytochrome P450 (CYP) 3A4 is the major enzyme responsible for the clearance of avacopan and the formation and clearance of the M1 metabolite.

Elimination

Based on population pharmacokinetic analysis, the total apparent body clearance (CL/F) of avacopan is 16.3 l/h (95% CI: 13.1-21.1 l/h). The median effective half-life is 36.8 hours (1.5 days) and the median terminal elimination half-life is 510 hours (21 days) based on population pharmacokinetic analysis. When avacopan is discontinued after steady state has been reached, the residual plasma concentration of avacopan is expected to decrease to ~20%,

<10% and <5% of the maximum steady state concentration in approximately 4 weeks, 7 weeks and 10 weeks after the last dose, respectively.

Following oral administration of radiolabelled avacopan, approximately 77% and 10% of the radioactivity was recovered in the faeces and urine, respectively, with 7% and less than 0.1% of the radioactive dose recovered as unchanged avacopan in the faeces and in the urine, respectively. These results suggest that the main route of clearance of avacopan is metabolism, followed by biliary excretion of metabolites in the faeces.

Kinetics in specific patient groups

Hepatic impairment

The pharmacokinetic properties of avacopan were evaluated in 16 patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. No significant changes in pharmacokinetics were observed compared to healthy volunteers. In subjects with mild or moderate liver function impairment, avacopan AUC (geometric mean) increased by 12% and 12% respectively (healthy: 1,220 ng•h/ml; mild: 1,370 ng•h/ml; moderate: 1,360 ng•h/ml), C_{max} (geometric mean) decreased by 13% and 17% respectively (healthy: 123 ng/ml; mild: 107 ng/ml; moderate: 102 ng/ml), compared to subjects with normal liver function. In subjects with mild or moderate liver function impairment, the AUC of the M1 metabolite increased by 11% and 18%, respectively (healthy: 799 ng•h/ml; mild: 885 ng•h/ml; moderate: 943 ng•h/ml), C_{max} decreased by 5% and 16%, respectively (healthy: 48.2 ng/ml; mild: 46.0 ng/ml; moderate: 40.4 ng/ml), compared to patients with normal liver function.
Avacopan has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

Renal impairment

In the phase III study, the estimated glomerular filtration rate (eGFR) ranges studied were <30 ml/min/1.73 m² (52 subjects), 30-59 ml/min/1.73 m² (56 subjects), >59 ml/min/1.73 m² (55 subjects). Based on population pharmacokinetic analysis, plasma exposure of avacopan is similar between patients with renal impairment and patients with normal renal function.

Avacopan has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

Elderly patients

In the phase III study, the age range of subjects was 13-83 years and 46 subjects (13.9%) were >75 years of age.
Population pharmacokinetic analysis revealed no significant effect of age (in adults) on plasma exposure to avacopan; however, pharmacokinetic data of clinical trials were limited for patients over 75 years of age.

Ethnicity
No clinically meaningful differences in plasma concentrations of avacopan and the M1 metabolite were observed according to ethnicity (Caucasian, Asian, or Black population).

Preclinical data

The non-clinical data do not indicate any particular hazard for humans based on conventional safety pharmacology and repeated dose toxicity studies.

Genotoxicity

Avacopan was not genotoxic based on the results of the bacterial mutagenicity (Ames test), mouse lymphoma (TK) and *in vivo* rat bone marrow micronucleus assays.

Carcinogenicity

The carcinogenic potential of avacopan was assessed in a 2-year study in rats and hamsters.

Avacopan was not carcinogenic in rats and hamsters at exposures from 3.7 to 6-fold the clinical dose.

Reproductive toxicity

Fertility and early embryonic development
Avacopan had no effect on male or female reproductive performance (fertility) or early development in hamsters at oral doses of up equivalent up to 6.8-fold the clinical AUC.

Embryofoetal development
Avacopan was not teratogenic when administered orally to hamsters and rabbits. In hamsters, an increased incidence of skeletal variations (short thoracolumbar supernumerary rib) was observed at exposure equivalent to 5.3-fold the clinical AUC. In rabbits, avacopan caused

maternal toxicity (adverse clinical signs and abortions), but no foetal toxicity at 0.6-fold the clinical AUC.

Pre- and post-natal development

Avacopan did not cause adverse reactions in the offspring of hamsters exposed to up to 6.3-fold the clinical AUC during the gestation and lactation periods until weaning. Analysis of avacopan plasma levels in lactating females and plasma levels in nursing pups revealed the presence of avacopan. This finding indicated that avacopan is likely secreted into the breast milk of lactating hamsters.

Other information

Shelf life

The medicinal product should not be used after the expiry date which is stated on the packaging after “EXP”.

Special precautions for storage

Store at 15-30 °C in its original packaging with the bottle closed and keep out of the reach of children.

Authorisation number

66772 (Swissmedic)

Packs

Each bottle contains 30 or 180 hard capsules (10 mg). [B]

Marketing authorisation holder

Vifor Fresenius Medical Care Renal Pharma Ltd., St-Gallen

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