swissmedic

Date: 29 January 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lyvdelzi

International non-proprietary name:	seladelpar
Pharmaceutical form:	capsule, hard
Dosage strength(s):	10 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Gilead Sciences Switzerland Sàrl
Marketing authorisation no.:	70063
Decision and decision date:	temporary authorisation in accordance with Art. 9a TPA approved on 9 December 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibody
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
BCS	Biopharmaceutics Classification System
CI	Confidence interval
CK	Creatine kinase
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	Food and Drug Administration (USA)
FGF-21	Fibroblast growth factor 21
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
LS	Least squares
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NRS	Numerical rating score
PBC	Primary biliary cholangitis
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPAR-δ	Peroxisome proliferator-activated receptor delta
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TB	Total bilirubin
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)
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for seladelpar (as seladelpar lysine dihydrate) in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 8 November 2024.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9*a* TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Lyvdelzi is indicated for the treatment of primary biliary cholangitis (PBC), including pruritus, in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.

This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

2.2.2 Approved indication

Lyvdelzi is indicated for the treatment of primary biliary cholangitis (PBC) in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA (see "Clinical Efficacy").

This indication was approved based on a reduction of alkaline phosphatase (ALP) (see "Properties/Effects"). Improvement in survival or prevention of liver decompensation events have not been demonstrated.

This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose of Lyvdelzi is 10 mg once daily.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	17 February 2025
Formal control completed	18 February 2025
List of Questions (LoQ)	24 April 2025
Response to LoQ	7 July 2025
Preliminary decision	26 August 2025
Response to preliminary decision	24 October 2025
Labelling corrections and/or other aspects	7 November 2025
Response to labelling corrections and/or other aspects	17 November 2025
Informal exchange regarding other aspects	25 November 2025
Response to informal exchange regarding other aspects	27 November 2025
Informal exchange regarding other aspects	28 November 2025
Response to informal exchange regarding other aspects	2 December 2025
Final decision	9 December 2025
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

Primary biliary cholangitis (PBC)

Primary biliary cholangitis (PBC)[1] previously known as primary biliary cirrhosis is a rare autoimmune disorder that leads to the gradual destruction of intrahepatic bile ducts resulting in periportal inflammation and cholestasis. Prolonged hepatic cholestasis subsequently leads to cirrhosis and portal hypertension.

PBC mostly affects women of middle age and is thought to be a disease of Europe and North America. Patients with PBC can be asymptomatic or may present with jaundice that is secondary to cholestasis, pruritus, and fatigue. Pruritus occurs in about 20% to 70% of patients, which is thought to be the neurocutaneous effect of retained bile salts. At later stages, PBC patients also have iron deficiency anaemia due to chronic blood loss secondary to portal hypertensive gastropathy, and patients who have already developed cirrhosis may have coagulopathy (elevated prothrombin time), thrombocytopenia, and leukopenia in addition to anaemia.

The pathogenesis of PBC is thought to be related to the interaction between genetic predisposition and environmental triggers. Environmental triggers include various xenobiotics from toxic waste, cigarette smoking, nail polish, hair dye, and some microorganisms (e.g. *Escherichia coli, Mycobacterium gordonae, Novosphingobium aromaticivorans*). These induce the autoimmune reaction in genetically susceptible patients, which is evident by the presence of a humoral and cellular response to an intracytoplasmic antigen, the presence of antimitochondrial antibody (AMA), and the involvement of T lymphocytes in the destruction of bile ducts. In addition, bacteria containing lipoylated proteins lead to immune response targeting their lipoylated proteins via molecular mimicry.

The diagnostic criteria for PBC include an absence of any other liver disease, no evidence of extrahepatic biliary obstruction on imaging, and at least 2 out of 3 of the following:

1. Elevation of alkaline phosphatase (ALP) at least 1.5 times upper limit of normal (ULN) for more than 6 months
2. Presence of AMA with a titre of 1:40 or higher
3. Histopathological evidence of PBC (nonsuppurative destructive cholangitis or "florid duct lesion" and destruction of interlobular bile ducts with a predominance of lymphocytic infiltration).

Liver biopsy is not required for diagnosis with typical clinical features and positive AMA but is helpful in disease prognosis and staging.

The most reliable indicators of a PBC patient's prognosis are the rise in serum bilirubin level and the Mayo risk score. If the bilirubin levels are consistently high, the survival is significantly reduced with an average survival of 1.7 years.

The goal of therapy in PBC is to prevent disease progression and manage the symptoms and complications related to chronic cholestasis. Ursodeoxycholic acid (UDCA) is the first-line therapy for management of PBC. It is a hydrophilic bile salt, which stabilises hepatocyte membranes against toxic bile salts and inhibits apoptosis and fibrosis. Patients benefit most when UDCA is started at an earlier stage, which has been shown to delay the progression of the disease and the development of cirrhosis. Cholestyramine, rifampicin, naltrexone, and antihistamines like diphenhydramine and hydroxyzine may be used symptomatically to reduce pruritus. Liver transplantation is the gold standard treatment for PBC. However, the disease can recur after transplantation, with a recurrence rate of up to 35%.

Retrospective analysis of a PBC register data based on 474 patients, representing about one third of the Swiss PBC population (assuming a prevalence of 15–20 cases per 100,000), showed that median age at diagnosis was 53 years, 84% were women, and 86% were AMA-positive[2]. Median follow up was 5.4 years. About 94% were treated with UDCA. The overall event-free[3] survival rate was 96% at 5

[1] Pandit S, Samant H. Primary Biliary Cholangitis. [Updated 2023 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459209/
[2] Terziroli Beretta-Piccoli, B., Stirnimann, G., Cerny, A. et al. Geoepidemiology of Primary Biliary Cholangitis: Lessons from Switzerland. Clinic Rev Allerg Immunol 54, 295–306 (2018). https://doi.org/10.1007/s12016-017-8656-x
[3] Events = liver transplantation or death from liver-related causes

years, 85% at 10 years, and 75% at 15 years. One quarter of patients and one half of male patients had splenomegaly at diagnosis, suggesting a diagnostic delay.

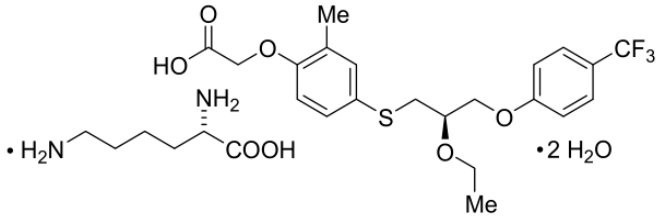
Seladelpar (Lyvdelzi®, Livdelzi®)

Seladelpar is a selective peroxisome proliferator-activated receptor delta (PPAR-δ) agonist. PPAR-δ is a nuclear receptor that is expressed ubiquitously in all tissues. PPAR-δ agonism alters lipid synthesis and metabolism and has anti-inflammatory effects in macrophages, including Kupffer cells. By activating PPAR-δ, seladelpar suppresses bile acid production through downregulation of CYP7A1 expression and stimulation of the fibroblast growth factor 21 (FGF-21) signalling pathway. This is expected to reduce cholestatic injury and improve bile acid homeostasis in patients with PBC.

4 Quality aspects

4.1 Drug substance

INN: Seladelpar
Chemical name: L-Lysine, [4-({(2R)-2-ethoxy-3-[4-(trifluoromethyl)phenoxy]propyl}sulfanyl)-2-methylphenoxy]acetate dihydrate
Molecular formula: $C_{21}H_{23}F_3O_5S \cdot C_6H_{14}N_2O_2 \cdot 2H_2O$
Molecular mass: 626.7 g/mol
Molecular structure:



The drug substance is a white to off-white solid, variable hydrate. Seladelpar exhibits pH-dependent solubility and was categorised as a Biopharmaceutics Classification System (BCS) Class II substance based on solubility and permeability data.

The synthetic process leads to the desired form.

Specifications include the relevant test parameters as recommended by the relevant ICH guidelines and compliant with the current Ph. Eur. The analytical methods are adequately described and the methods validated.

Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug product

The drug product is an immediate-release hard capsule for oral administration containing 10 mg of seladelpar. Seladelpar capsules have a light gray opaque body and dark blue opaque cap, with “10” imprinted in black ink on the body and “CBAY” imprinted in white ink on the cap.

The manufacturing process consists of standard unit operations and leads to appropriate quality.

Specifications include the relevant test parameters as recommended by the relevant ICH guidelines and compliant with the current Ph. Eur. The analytical methods are adequately described and the methods validated.

Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines.

4.3 Quality conclusions

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

5 Nonclinical aspects

For the review of the marketing authorisation application (MAA) for Lyvdelzi, the division Nonclinical Assessment at Swissmedic conducted an abridged evaluation, which was essentially based on the CHMP assessment report of the EMA dated 12 December 2024 (EMA/CHMP/548658/2024) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Lyvdelzi in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA and FDA. The available assessment reports and respective product information from EMA and FDA were used as a basis for the clinical pharmacology evaluation.

The pharmacology of seladelpar has been sufficiently characterised. Limited data in patients with compensated cirrhosis and in patients with end-stage renal disease preclude the use in these subpopulations. Seladelpar has a potential for clinically relevant interactions with other drugs. For details concerning clinical pharmacology see the Information for healthcare professionals in the appendix of this report.

6.2 Dose finding and dose recommendation

Phase 2 Study CB8025-21528 was the first clinical study of the seladelpar development programme for the treatment of PBC. It was a 1:1:1 randomised, placebo-controlled study that evaluated 2 doses of seladelpar (50 mg and 200 mg/day) over a 12-week period in patients with PBC who had inadequate response to UDCA. The study was designed to demonstrate efficacy of seladelpar versus placebo in terms of change in ALP level from baseline to the end of treatment, as well as to assess the safety and tolerability of seladelpar. The study was stopped after 41 patients (approximately 55% of the planned 75) had enrolled because the stopping rule of Grade 3 ALT/AST elevations was met for 3 subjects receiving seladelpar: 2 in the 200 mg and 1 in the 50 mg group. In addition, one patient receiving seladelpar 200 mg discontinued treatment because of myopathy (peak CK 4,062 U/L) and a Grade 3 AST elevation. In terms of efficacy, both seladelpar treatment groups showed significantly greater reductions in ALP levels from baseline to the end of treatment as did placebo group. No dose of seladelpar was significantly superior over the other.

Subsequently, lower doses were studied in Study CB8025-21629. This was an 8-week, dose-ranging, open-label, randomised, phase 2 study with a 44-week extension to evaluate the safety and efficacy of seladelpar in patients with PBS and an inadequate response or intolerance to UDCA. Patients were to receive oral doses of 2, 5, 10, 15 and 20 mg seladelpar once daily. Based on interim analysis results, doses above 10 mg were not administered. Patients were randomised to 2 mg (11 patients), 5 mg (53 patients) and 10 mg (55 patients) treatment groups only.

The primary efficacy endpoint of mean (95% confidence intervals [CIs]) percent change in ALP from baseline to Week 8 was -26.1% (-32.2%, -19.9%), -33.4% (-38.6%, -28.1%), and -41.4% (-45.1%, -37.7%) in the 2, 5, and 10 mg dose groups, respectively. The change in the 10 mg dose group was significantly different from the change in the 2 mg dose group ($p = 0.0021$) and the 5 mg dose group ($p = 0.0024$). ALP normalisation rates at Week 12 were 0%, 10.6%, and 31.4% for the 2, 5 and 10 mg dose groups, respectively. The effect lasted for 52 weeks, with the 10 mg dose achieving the best results, justifying the selection of the 10 mg dose for further development.

At substantially lower doses than those evaluated in the initial dose-finding trial CB8025-21528, study CB8025-21629 showed similar safety findings but with a lower intensity level compared to study CB8025-21528. These were transaminase increases (Grade ≥2) in 10 patients as well as elevated CK levels in 4 patients. Also, it is worth noting that elevations in pancreatic enzymes (amylase or lipase) were reported in 4 patients, and one patient experienced a Grade 4 angina pectoris event.

Study CB8025-31735 – a phase 3 double-blind, randomised, placebo-controlled trial supported the dose finding between seladelpar 5 mg and 10 mg in PBC. This study was terminated early due to liver safety concerns in a phase 2 trial in non-alcoholic steatohepatitis, which on further investigation were determined to be findings present at baseline and not reflective of liver injury. The primary endpoint (decrease in ALP level) in Study CB8025-31735 was revised to a Month 3 (Week 12) instead of a Month 12, and analyses were done on a reduced patient collective. Both seladelpar doses of 5 mg and

10 mg met the primary endpoint after 12 weeks compared to placebo, while superior efficacy of seladelpar 10 mg over seladelpar 5 mg was demonstrated. The key secondary endpoint of pruritus reduction was also met for the 10 mg dose. There was no imbalance regarding safety between the groups, although Study CB8025-31735 was substantially shortened.

Overall, these results justify seladelpar 10 mg as the optimal dose for both safety and efficacy to be investigated in the pivotal trial.

6.3 Efficacy

The efficacy of seladelpar in PBC was assessed in a single phase 3 study CB8025-32048. This was an international, 2:1 randomised, double-blind, placebo controlled, parallel-arm study. Adult patients with confirmed PBC and inadequate response, or intolerance, to UDCA with ALP ≥ 1.67× ULN and total bilirubin ≤ 2× ULN were eligible for participation. Patients with advanced PBC as defined by the Rotterdam criteria or presence of clinically relevant hepatic decompensation or other liver disease were excluded. Study drug – seladelpar 10 mg or placebo – was administered once daily for up to 12 months as an oral capsule.

Overall, 193 PBC patients (128 seladelpar, 65 placebo) were randomised. Baseline characteristics were generally balanced between the treatment arms. Notably, mean baseline total bilirubin values were below ULN, and the percentage of patients with total bilirubin > ULN was 15.6% and 7.7% in the seladelpar and placebo arms, respectively.

The study met its primary efficacy endpoint of the composite biochemical response, defined as ALP < 1.67× ULN, ≥15% reduction in ALP, and total bilirubin ≤ ULN at Month 12. A significantly higher percentage of patients receiving seladelpar (61.7%; 79/128) achieved the primary efficacy endpoint compared to placebo (20.0%; 13/65) (p < 0.0001). At Month 12, 65.6% of patients in the seladelpar arm compared with 26.2% in the placebo arm achieved the ALP < 1.67× ULN component of the primary endpoint. In addition, a higher percentage of patients receiving seladelpar (83.6%) experienced a decrease from baseline of ≥15% in ALP levels, compared with patients who received placebo (32.3%). The percentage of patients with total bilirubin ≤ ULN was 81.3% and 76.9% in the seladelpar and placebo arms, respectively. Higher percentages of responders in the seladelpar arm compared with placebo were observed as early as Month 1, and these differences were maintained with ongoing treatment throughout the course of the study. This result was confirmed in sensitivity analyses.

The study also met the key secondary efficacy endpoint of ALP normalisation (ALP ≤ ULN) at Month 12. A significantly higher percentage of patients in the seladelpar arm (25%) achieved ALP normalisation compared with the placebo arm (0%) (p <0.0001). As for the primary endpoint, a beneficial effect of seladelpar was already observed at Month 1 and maintained throughout the course of the study. This result was also confirmed in sensitivity analyses.

The second key secondary endpoint of change in the pruritus numerical rating score (NRS) at Month 6 in patients with moderate to severe pruritus at baseline (Pruritus NRS ≥4) was also met. Seladelpar treatment led to a statistically significant improvement in Pruritus NRS compared with placebo with a LS (least squares) mean change of -3.2 vs -1.7, respectively (p=0.0047). However, the second key secondary endpoint was predefined at Month 6 instead of Month 12 as for the primary and first secondary endpoints. Therefore, whether the effect on pruritus is maintained up to 12 months remains unknown. Additionally, with -1.5 points difference between the treatment arms, the effect on pruritus was less pronounced than the -2.0-difference assumed for the sample size calculation.

Among patients with ALP ≥ 350 U/L and Pruritus NRS <4 at baseline a proportion of biochemical responders was lower in the seladelpar arm (13.3%, 2 out of 15 patients) as compared to the placebo arm (22.2%, 2 out of 9 patients). Also, no ALP normalisation (0.0%) in patients with baseline ALP ≥350 U/L was found in either group (seladelpar or placebo) regardless of the Pruritus NRS baseline status. However, the response differences observed in this stratum should be interpreted with caution, given the small sample size and the fact that patients with markedly elevated baseline ALP values required greater absolute reductions to meet the ALP <1.67× ULN component of the composite biochemical response endpoint.

According to current guidelines, the biochemical surrogate endpoint is acceptable for the temporary approval. However, placebo-controlled long-term data on liver-related clinical outcomes and overall survival must be generated as soon as possible. Study CB8025-41837, the results of which are expected in February 2030, is planned to investigate the long-term clinical benefit of seladelpar treatment in PBC.

6.4 Safety

The safety of seladelpar was evaluated based on data from the pivotal trial (Study CB8025-32048), supplemented by additional data from the earlier placebo-controlled PBC trial (Study CB8025-31735) and long-term open-label supportive data. The most common adverse events were gastrointestinal symptoms (abdominal pain, abdominal distention, and nausea) and headache and did not lead to treatment discontinuation. Serious adverse advents were similar across the seladelpar and placebo arms in Study CB8025-32048. Fractures occurred in 5 (4%) patients in the seladelpar-treated arm versus none in placebo. Liver test abnormalities (elevated ALT and AST values) were observed with higher doses (5 and 20 times the marketed dose) and were not associated with elevations in total bilirubin (TB) or clinical symptoms of liver injury. These liver test abnormalities were not observed with the 10 mg dose, and no prohibitive safety signals were identified in the pivotal phase 3 study, although the safety database was limited.

6.5 Final clinical benefit risk assessment

PBC is a life-threatening disorder with limited treatment options. Based on the review of all available efficacy and safety data, the benefits of seladelpar 10 mg outweigh the risks of PBC treatment in combination with UDCA in adult patients who have an inadequate response to UDCA, or as monotherapy in patients who do not tolerate UDCA.

Continued approval for this indication is contingent upon the demonstration of sustained long-term clinical benefit with an acceptable safety profile.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Lyvdelzi 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 valid and relevant reference document 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. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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.
Lyvdelzi has been authorised temporarily, see “Indications/Uses” section.

LYVDELZI®

Composition

Active substances

Seladelpar as seladelpar lysine dihydrate

Excipients

Capsule content: microcrystalline cellulose, mannitol, croscarmellose sodium, butyl hydroxytoluene, magnesium stearate, colloidal silicon dioxide.
Capsule shell: gelatin, titanium dioxide, black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), indigo carmine (E132).
Black ink used to imprint “10” (on the body of the capsule shell contains): shellac (E904), propylene glycol (E1520), potassium hydroxide (E525), black iron oxide (E172).
White ink used to imprint “CBAY” (on the cap of the capsule contains): shellac (E904), propylene glycol (E1520), sodium hydroxide (E524), povidone (E1201), titanium dioxide.

One hard capsule of Lyvdelzi contains 0.42 mg sodium.

Pharmaceutical form and active substance quantity per unit

Hard capsule containing seladelpar lysine dihydrate equivalent to 10 mg seladelpar.
Opaque, hard gelatine capsules with dark blue opaque cap and a light grey opaque body imprinted with “CBAY” in white ink on the cap and “10” in black ink on the body.

Indications/Uses

Lyvdelzi is indicated for the treatment of primary biliary cholangitis (PBC) in adults in combination with ursodeoxycholic acid (UDCA) who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA (see “Clinical Efficacy”).
This indication was approved based on a reduction of alkaline phosphatase (ALP) (see “Properties/Effects”). Improvement in survival or prevention of liver decompensation events have not been demonstrated.

This indication has been granted temporary authorisation as the documentation was incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is

contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an authorisation without special conditions.

Dosage/Administration

Recommended Dosage

The recommended dose of Lyvdelzi is 10 mg taken once daily.

Mode of administration

Oral use.
The hard capsules can be taken with or without food.

Missed dose

If a dose of Lyvdelzi is missed, the patient should take the subsequent dose at the next scheduled time point. A double dose should not be taken to make up for a missed dose.

Special dosage instructions

Patients with hepatic impairment

No dose adjustment of Lyvdelzi is required in patients with mild hepatic impairment (Child-Pugh A). The safety and efficacy of Lyvdelzi in patients with decompensated cirrhosis (Child-Pugh B or C) have not been established. Use of Lyvdelzi is not recommended in patients who have or develop decompensated cirrhosis (see “Pharmacokinetics”).

Monitor patients with cirrhosis for evidence of decompensation. Treatment with Lyvdelzi should be discontinued if the patient progresses to moderate or severe hepatic impairment (Child-Pugh B or C) (see “Warnings and Precautions”).

Patients with renal impairment

No dose adjustment of Lyvdelzi is required in patients with mild (estimated glomerular filtration rate (eGFR) ≥ 60 to < 90 mL/min), moderate (eGFR ≥ 30 to < 60 mL/min), or severe (eGFR < 30 mL/min) renal impairment. Lyvdelzi has not been studied in patients with end stage renal disease (ESRD) on dialysis, therefore no dosage recommendation can be given for these patients (see “Pharmacokinetics”).

Elderly patients

No dose adjustment is required for patients aged 65 years or older (see “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Lyvdelzi in children and adolescents have not been demonstrated. Lyvdelzi is not authorised for use in children and adolescents.

Administration modification in therapy with bile acid binding resins

Administer Lyvdelzi at least 4 hours before or 4 hours after taking bile acid binding resins, or at as great an interval as possible (see “Interactions”).

Contraindications

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

Warnings and precautions

Liver test abnormalities

Lyvdelzi has been associated with dose related increases in serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) levels greater than 3-times upper limit of normal (ULN) in patients with PBC receiving 50 mg once daily (5 times higher than the recommended dosage) and 200 mg (20-times higher than the recommended dosage) once daily. Transaminase levels returned to pretreatment levels upon Lyvdelzi discontinuation. Lyvdelzi 10 mg once daily did not show a similar pattern for increase in transaminase levels (see “Overdose”).

Obtain baseline clinical and laboratory assessments at initiation of treatment with Lyvdelzi and monitor thereafter according to routine patient management. Interrupt Lyvdelzi treatment if the liver tests (ALT, AST, total bilirubin [TB], and/or alkaline phosphatase [ALP]) worsen, or the patient develops signs and symptoms consistent with clinical hepatitis (e.g. jaundice, right upper quadrant paint, eosinophilia). Consider permanent discontinuation if liver tests worsen after restarting Lyvdelzi.

Biliary Obstruction

Avoid use of Lyvdelzi in patients with complete biliary obstruction. If biliary obstruction is suspected, interrupt Lyvdelzi and treat as clinically indicated.

Fractures

Fractures occurred in 3.9% (n=5) of Lyvdelzi-treated patients compared to 0% in placebo-treated patients in the pivotal study CB8025-32048 (see “Undesirable effects”).
Consider the risk of fracture in patients treated with Lyvdelzi and monitor bone health according to current standards of care.

Co-administration of other medicinal products

Co-administration of probenecid with Lyvdelzi is not recommended (see ”Interactions”).
Co-administration of Lyvdelzi with both ciclosporin and fluconazole is not recommended (see “Interactions”).

Excipients

Lyvdelzi contains less than 1 mmol (23 mg) sodium per hard capsule, which means it is almost “sodium-free”.

Interactions

Effect of other medicinal products on seladelpar

Probenecid

Concomitant administration of seladelpar with probenecid (an OAT3 and OATP1B3 inhibitor) may increase seladelpar exposure. Concomitant administration of seladelpar with probenecid is not recommended (see “Warnings and precautions”).

In a dedicated clinical drug interaction study, seladelpar $AUC_{0\text{-}inf}$ increased by 2-fold and C_{max} by 4.69-fold following concomitant use of a single 10 mg seladelpar dose with 500 mg probenecid in healthy subjects.

Combination of drug transporters and CYP2C9- and CYP3A4-inhibitors

When seladelpar is administered concomitantly with ciclosporin (a BCRP, OATP1B1, OATP1B3 and CYP3A4 inhibitor) and fluconazole (a moderate CYP2C9 and CYP3A4 inhibitor), a marked increase in seladelpar exposure (by more than five times) is expected. The concomitant use of such a combination is not recommended (see “Warnings and precautions”).

Inhibitors of drug transporters

Concomitant administration of seladelpar with dual or multiple clinical inhibitors of drugs transporters including BCRP, OATP1B1, OATP1B3 and OAT3 (e.g cyclosporine) may result in an increase of seladelpar exposure. When seladelpar is concomitantly administered with dual or multiple clinical inhibitors of drugs transporters including BCRP, OATP1B1, OATP1B3, and OAT3, patients should be closely monitored for adverse effects.
In a dedicated clinical drug interaction study, seladelpar $AUC_{0\text{-}inf}$ increased by 2.1-fold and C_{max} by 2.9-fold following concomitant use of a single 10 mg seladelpar dose with 600 mg cyclosporine (a BCRP, OATP1B1, OATP1B3 and CYP3A4 inhibitor) in healthy subjects.

CYP2C9 and CYP3A4 inhibitors

Seladelpar is primarily metabolized *in vitro* by CYP2C9 and to a lesser extent by CYP2C8 and CYP3A4. Concomitant administration of seladelpar with medicinal products that are strong CYP2C9 inhibitors, or dual moderate CYP2C9 and moderate-to-strong CYP3A4 inhibitors, may result in an increase in seladelpar exposure. When seladelpar is concomitantly administered with medicinal products that are strong CYP2C9 inhibitors (e.g. fluconazole, mifepristone), or dual moderate CYP2C9 and moderate to strong CYP3A4 inhibitors, patients should be monitored for adverse effects.

In a dedicated clinical drug interaction study, seladelpar $AUC_{0\text{-}inf}$ increased by 2.4-fold and C_{max} by 1.4-fold following concomitant use of a single 10 mg seladelpar dose with 400 mg fluconazole (moderate CYP2C9 and CYP3A4 inhibitor) in healthy subjects.

CYP2C9 inducers and strong CYP3A4 inducers

Concomitant administration of seladelpar with medicines that are CYP2C9 inducers and strong CYP3A4 inducers (e.g. rifampicin, a strong CYP3A4 and moderate CYP2C9 inducer) can decrease seladelpar exposure. When seladelpar is concomitantly administered with medicinal products that are CYP2C9 inducers and strong CYP3A4 inducers, patients should be monitored for a potential reduction in efficacy. Seladelpar $AUC_{0\text{-}inf}$ decreased by approximately 44% and C_{max} by 24% following administration of a single 10 mg seladelpar dose after carbamazepine 300 mg twice daily in healthy subjects. The carbamazepine (a strong CYP3A and weak CYP2C9 inducer) dose was escalated from 100 mg to 300 mg over 7 days.

Bile acid binding resins

Bile acid binding resins such as cholestyramine, colestipol, or colesevelam, may reduce the absorption of other medicinal products administered concurrently. Seladelpar should be taken at least 4 hours before or 4 hours after taking a bile acid binding resin.

Quinidine

Seladelpar exposures were not significantly altered when a single dose of 600 mg quinidine (a P-gp inhibitor) was co-administered in healthy subjects.

Effect of seladelpar on other medicinal products

Seladelpar has no clinically relevant effect on the pharmacokinetics of tolbutamide (a CYP2C9 substrate), midazolam (a CYP3A4 substrate), simvastatin (a CYP3A4 and OATP substrate), atorvastatin (a CYP3A4 and OATP substrate), and rosuvastatin (an OATP and BCRP substrate).

In vitro Studies

Based on *in vitro* studies, it is expected that a dose of 10 mg seladelpar does not significantly affect the pharmakokinetics of concomitant drugs that are substrates of CYP enzymes (1A2, 2B6, 2C8, 2C19, 2D6), UGTs, P-gp, MATEs, OCT1, OCT2, OAT1, or OAT3.

Seladelpar is a substrate of OATP1B1, OATP1B3, BCRP, P-gp, and OAT3 transporters *in vitro*. Seladelpar is not a substrate of MATE1, MATE2-K, OAT1, OCT1, or OCT2.

Pregnancy, lactation

Pregnancy

There are no or very limited amount of data (less than 300 pregnancy outcomes) from the use of seladelpar in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see ”Preclinical data”).
As a precautionary measure**,** it is preferable to avoid the use of Lyvdelzi during pregnancy.

Lactation

It is not known whether seladelpar or its metabolites are excreted in breast milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Lyvdelzi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of seladelpar on fertility are available. Animal studies do not indicate any direct or indirect effects on fertility or the ability to reproduce (see “Preclinical data”).

Effects on ability to drive and use machines

No studies on the effects of seladelpar on the ability to drive and use machines have been performed.

Undesirable effects

Summary of the safety profile

Assessment of adverse reactions is based on data from a pivotal 52-week, 2:1 randomised, placebo-controlled clinical trial (CB8025-32048) with 193 PBC patients, of whom 128 patients were treated with 10 mg seladelpar, and additionally supported by another prematurely terminated 52-week placebo-controlled clinical (CB8025-31735) that investigated both 5 mg and 10 mg seladelpar. A total of 217 PBC patients were treated with 10 mg seladelpar once daily in both trials.

Based on clinical trial experience, the most frequently reported adverse reactions were abdominal pain (11.5%), headache (7.8%), nausea (6.9%), abdominal distension (5.1%) and anaemia (3.2%). These adverse reactions were non-serious and did not lead to discontinuation of seladelpar.

List of undesirable effects

The adverse reactions are listed below in Table 1 according to MedDRA system organ classes and sorted by decreasing frequency. Frequencies are defined as very common (≥ 1/10) and common (≥ 1/100 to < 1/10).

Table 1: Tabulated list of adverse reactions with Lyvdelzi

Frequency[a]	Adverse reaction
Blood and lymphatic system disorders	
Common	Anaemia
Nervous system disorders	
Common	Headache
Gastrointestinal disorders	
Very common	Abdominal pain[b] (11.5%)
Common	Nausea
Common	Abdominal distension

[a] Frequency based on all patients receiving 10 mg seladelpar in CB8025-32048 and CB8025-31735.
[b] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

Additional information

Fractures

In the pivotal study CB8025-32048, fractures occurred in 3.9% (n=5) of Lyvdelzi-treated patients compared to 0% in placebo-treated patients. Baseline bone mineral density was not obtained. The median time to fracture after starting treatment with Lyvdelzi was 295 days (range: 89–349).

Laboratory Changes

Serum Creatinine

Dose dependent increases in serum creatinine and decreases in eGFR have been observed more frequently in Lyvdelzi-treated patients compared to placebo-treated patients. In trial CB8025-32048, median increases in serum creatinine of up to 6.6% were observed with the 10 mg dose compared with up to 2.2% in patients taking placebo. Ten percent (N=12) of Lyvdelzi-treated patients had a decline in eGFR of at least 25%, compared to 2% (N=1) of placebo-treated patients. None of the patients experienced an eGFR decline of 50% or more. Increases in serum creatinine were not progressive and returned towards baseline with ongoing Lyvdelzi treatment, except for 2 patients in trial CB8025-32048. None of the patients required discontinuation of Lyvdelzi and there were no clinical findings associated with the observed changes in serum creatinine.

Reporting of suspected adverse reactions

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 asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

PBC patients who received 5-times the recommended dosage or 20-times the recommended dosage of Lyvdelzi experienced an increase in liver transaminases, muscle pain, and/or elevations in creatine phosphokinase, which resolved upon Lyvdelzi discontinuation (see “Warnings and Precautions”).

There is no specific treatment for overdose with Lyvdelzi. General supportive care of the patient is indicated, as appropriate. If indicated, elimination of unabsorbed medicinal product should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because seladelpar is highly bound to plasma proteins, haemodialysis should not be considered.

Properties/Effects

ATC code

A05AX07

Mechanism of action

Seladelpar is a peroxisome proliferator-activated receptor delta (PPARδ) agonist, or delpar. PPARδ is a nuclear receptor expressed in the liver and other tissues. PPARδ activation reduces bile acid synthesis in the liver through Fibroblast Growth Factor 21 (FGF21)-dependent downregulation of CYP7A1, the key enzyme for the synthesis of bile acids from cholesterol, and by decreasing cholesterol synthesis and absorption.

Pruritus is a common symptom in patients with PBC, but its origins are not completely understood. Seladelpar treatment has been shown to reduce pruritus.

Pharmacodynamics

In controlled clinical studies, seladelpar treatment resulted in reduction of ALP, a biomarker of cholestasis. ALP reduction was observed within 1 week of treatment initiation, continued to decrease through Month 3, and was sustained through Month 12.

Cardiac electrophysiology

At 20-times the recommended dose of 10 mg, seladelpar did not cause clinically significant QTc interval prolongations.

Clinical efficacy

Trial CB8025-32048 - RESPONSE

The efficacy of Lyvdelzi was evaluated in CB8025-32048, a 52-week, randomized, double-blind, placebo-controlled trial. The trial included 193 adult patients with PBC with an inadequate response or intolerance to UDCA. Patients were included in the trial if their ALP was greater than or equal to 1.67-times the ULN and total bilirubin (TB) was less than or equal to 2-times the ULN. Patients were excluded from the trial if they had other chronic liver diseases, clinically important hepatic decompensation including portal hypertension with complications, or cirrhosis with complications (e.g., Model for End Stage Liver Disease [MELD] score of 12 or greater, known esophageal varices or history of variceal bleeds, history of hepatorenal syndrome).

Patients were randomized (2:1) to receive Lyvdelzi 10 mg (N=128) or placebo (N=65) once daily for 12 months. Lyvdelzi or placebo was administered in combination with UDCA in 181 (94%) patients during the trial, or as a monotherapy in 12 (6%) patients who were unable to tolerate UDCA.

The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. The mean age of patients was 57 years (Range: 28 to 75); 95% were female; 88% were White, 6% Asian, 2% Black or African American, and 3% American Indian or Alaska Native. Twenty-nine percent of the patients, 23% in the Lyvdelzi 10 mg arm and 42% in the placebo arm, identified as Hispanic/Latino.

At baseline, 18 (14%) of the Lyvdelzi-treated patients and 9 (14%) of the placebo-treated patients met at least one of the following cirrhosis criteria: Fibroscan > 16.9kPa; historical biopsy or radiological evidence suggestive of cirrhosis; platelet count < 140,000/μL with at least one additional laboratory finding including serum albumin < 3.5 g/dL, INR > 1.3, or TB > 1-time ULN; or clinical determination of cirrhosis by the investigator. All cirrhosis patients had Child-Pugh A status at baseline.

The mean baseline ALP concentration was 314 units per liter (U/L) (Range: 161 to 786), corresponding to 2.7-times ULN. The mean baseline TB concentration was 0.8 mg/dL (Range: 0.3 to 1.9) and was less than or equal to the ULN in 87% of the patients. Other mean baseline liver biochemistries were 48 U/L (Range: 9 to 115) for ALT, corresponding to 1.2-times the ULN; 40 U/L (Range: 16 to 94) for AST, corresponding to 1.2-times the ULN; and 288 U/L (Range: 42 to 1088) for gamma glutamyl transferase (GGT), corresponding to 1.7-times the ULN.

Lyvdelzi demonstrated significantly greater improvement on biochemical response and ALP normalization at Month 12 compared to placebo. Treatment with Lyvdelzi led to a significantly higher percentage of patients (62%) achieving the primary efficacy endpoint of composite biochemical response at Month 12 compared with placebo (20%) ($p < 0.0001$). The ULN for ALP was defined as 116 U/L. The ULN for TB was defined as 1.1 mg/dL. Table 2 presents results at Month 12 for the percentage of patients who achieved biochemical response, achieved each component of biochemical response, and achieved ALP normalisation. Overall, 87% of patients had a baseline of TB concentration less than or equal to ULN at baseline. Therefore, improvement in ALP was the main contributor to the biochemical response rate results at Month 12.

Table 1: Trial CB8025-32048: Composite biochemical endpoint and ALP normalisation with Lyvdelzi With or Without UDCA

	Lyvdelzi 10 mg (N=128)	Placebo (N=65)	Treatment Difference % (95% CI)[d]
Primary Composite Endpoint at Month 12			
Biochemical Response Rate, n (%)[a, b] [95% CI]	79 (62) [53, 70]	13 (20) [10, 30]	42 (28, 53) p < 0.0001
Components of Biochemical Response			
ALP less than 1.67-times ULN, n (%)	84 (66)	17 (26)	39 (25, 52)
Decrease in ALP of at least 15%, n (%)	107 (84)	21 (32)	51 (37, 63)
TB less than or equal to ULN, n (%)	104 (81)	50 (77)	4 (-7, 17)
ALP Normalisation, n (%)[b, c] **[95% CI]**	32 (25) [18, 33]	0 (0) [0, 0]	25 (18, 33) p < 0.0001

Patients who discontinued treatment prior to Month 12 or who had missing data were considered as non-responders.

[a] Biochemical response is defined as ALP less than 1.67-times ULN, an ALP decrease of greater than or equal to 15%, and TB less than or equal to ULN.

[b] P-values were obtained using the Cochran–Mantel–Haenszel test stratified by baseline ALP level (< 350 U/L versus ≥ 350 U/L) and baseline pruritus Numerical Rating Scale (NRS) (< 4 versus ≥ 4).

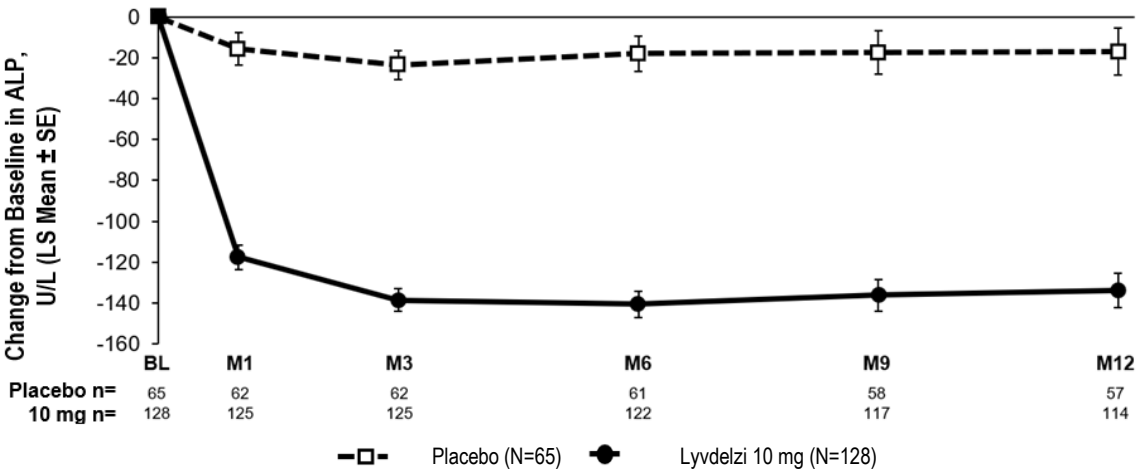
[c] ALP normalization is defined as ALP less than or equal to ULN.

[d] 95% unstratified Miettinen and Nurminen confidence intervals (CIs) are provided.

Liver Biochemistries

Figure 1 shows the mean reductions in ALP over 12 months in Lyvdelzi-treated patients compared to placebo-treated patients. Reductions were observed at Month 1, continued through Month 6, and were sustained through Month 12. The Least Squares (LS) mean (SE) change from baseline in ALP at Month 12 was -134 (-151, -117) U/L and -17 (-40, 6) U/L in the Lyvdelzi 10 mg and placebo arms, respectively.

Figure 1. Change from Baseline in ALP over 12 Months in Trial CB8025-32048 by Treatment Arm with or without UDCA[a]



[a] In trial CB8025-32048, there were 12 patients (6%) who were intolerant to UDCA and initiated treatment as monotherapy: 8 patients (6%) in the Lyvdelzi 10 mg arm and 4 patients (6%) in the placebo arm.

Among the subset of patients with ALP < 350 U/L at baseline, 76% (71/93) and 23% (11/47) of patients achieved a response at Month 12, in the Lyvdelzi 10 mg and placebo arms, respectively. For

patients with ALP ≥ 350 U/L at baseline, 23% (8/35) and 11% (2/18) of patients achieved a response at Month 12, in the Lyvdelzi 10 mg and placebo arms, respectively.

Pruritus

Lyvdelzi significantly reduced pruritus compared to placebo at Month 6 in patients with baseline average pruritus scores ≥ 4 as assessed by the pruritus NRS, a key secondary endpoint in trial CB8025-32048 (Table 3). A single-item patient-reported outcome (PRO), the pruritus Numerical Rating Scale (NRS), evaluated patients' daily worst itching intensity on an 11-point rating scale with scores ranging from 0 ("no itching") to 10 ("worst itching imaginable") in trial CB8025-32048. The pruritus NRS was administered daily in a 14-day run-in period prior to randomisation through Month 6. Table 3 presents the results of the comparison between Lyvdelzi and placebo on this endpoint evaluating the change from baseline in pruritus score at Month 6 in patients with baseline average pruritus scores greater than or equal to 4. The baseline average pruritus score for each patient was calculated by averaging the pruritus NRS scores administered in the run-in period and on Day 1 before treatment initiation. The pruritus scores at Month 6 for each patient were calculated by averaging the pruritus NRS scores within the last week in the month. Patients treated with Lyvdelzi demonstrated greater improvement in pruritus compared with placebo.

Table 2: Change from Baseline in Pruritus Score at Month 6 in in PBC Patients with Baseline Average Pruritus Score ≥ 4 in Trial CB8025-32048[a]

		Lyvdelzi 10 mg (N=49)	Placebo (N=23)	Treatment Difference % (95% CI)
Baseline Average Pruritus Score, Mean (SD) [b]		6.1 (1.4)	6.6 (1.4)	-
	Change from Baseline in Pruritus Score at Month 6[c]			
Mean (SE)		-3.2 (0.28)	-1.7 (0.41)	-1.5 (-2.5, -0.5) p < 0.005

[a] Assessed using the pruritus NRS, which evaluated patients' daily worst itching intensity on a 11-point rating scale with scores ranging from 0 ("no itching") to 10 ("worst itching imaginable"). The pruritus NRS was administered daily in a ≥ 14-day run-in period prior to randomization through Month 6. Moderate to severe pruritus was defined as a pruritus NRS score ≥ 4.

[b] Baseline included mean of all daily recorded scored during the run-in period and on Day 1. The pruritus scores for each patient post baseline months were calculated by averaging the pruritus NRS scores within the scheduled week each month.

[c] Based on LS means from a mixed-effect model for repeated measures (MMRM) for change from baseline at Months 1 (Week 4), 3 (Week 12), and 6 (Week 26) accounting for baseline average pruritus score, baseline ALP level (< 350 U/L versus ALP level ≥ 350 U/L), treatment arm, time (in months), and treatment-by-time interaction.

Pharmacokinetics

Absorption

Following oral administration of a single dose of Lyvdelzi 10 mg, the median time to peak concentration (T_{max}) was 1.5 hours for seladelpar. Seladelpar systemic exposure increased dose-proportionally from 2 mg (0.2 times the recommended dosage) to 15 mg (1.5 times the recommended dosage) and greater than dose proportionally at higher doses. For a dose increase from 10 mg to 200 mg (20 times the recommended dosage), mean C_{max} and mean AUC for seladelpar increased 70-fold and 27-fold, respectively.

Following once daily dosing, seladelpar steady-state was achieved by Day 4 and AUC increase was less than 30%. In PBC patients, median (CV) C_{max} and AUC for seladelpar was 90.5 (42.5%) ng/mL and 817 (44%) ng*h/mL, respectively at steady state following once daily dosing of 10 mg.

Co-administration of seladelpar with food delayed the t_{max} by 2.5 hours relative to fasted conditions and resulted in an approximately 32% reduction in the C_{max} of seladelpar. As the overall exposure (AUC) is similar, the effects of food on seladelpar pharmacokinetics are not considered clinically relevant.

Distribution

In PBC patients, seladelpar steady state apparent volume of distribution was approximately 110.3 L. Seladelpar plasma protein binding is greater than 99%.

Metabolism

Seladelpar is primarily metabolized in vitro by CYP2C9 and to a lesser extent by CYP2C8 and CYP3A4, resulting in the three major metabolites: seladelpar sulfoxide (M1), desethyl-seladelpar (M2), and desethyl-seladelpar sulfoxide (M3). The metabolite-to-parent AUC ratios were 0.36, 2.32 and 0.63 for M1, M2 and M3, respectively. Median T_{max} for metabolites were 10 hours for M1 and 4 hours each for M2 and M3. M1, M2 and M3 are not expected to have clinically relevant pharmacological effects.

Elimination

In PBC patients, the apparent oral clearance of seladelpar is 12.6 L/h. Following administration of a single dose of 10 mg seladelpar in healthy subjects, mean elimination half-life was 6 hours for seladelpar. In PBC patients, the half-life range was 3.8 to 6.7 hours for seladelpar.

Seladelpar is primarily eliminated in urine as metabolites. Following a single oral dose of 10 mg radiolabeled seladelpar in humans, approximately 73.4% of the dose was recovered in urine (less

than 0.01% unchanged) and 19.5% in feces (2.02% unchanged) within 216 hours. Biliary excretion of seladelpar was suggested by an animal study.

Pharmacokinetics in specific patient groups

Age, weight, gender and ethnicity

No clinically significant differences in the pharmacokinetics of seladelpar were observed based on age (19 to 79 years old), weight (45.8 to 127.5 kg), sex, and race (White, Black, Asian, or other).

Hepatic impairment

In a clinical pharmacology study in subjects with mild, moderate, and severe hepatic impairment of various causes (Child-Pugh A, B, and C, respectively), seladelpar AUC was increased 1.10, 2.52, and 2.12-fold, and C_{max} was increased 1.33, 5.19, and 5.03-fold, respectively, compared to subjects with normal hepatic function.
In an additional study, seladelpar exposures (C_{max}, AUC) were 1.7 to 1.8-fold higher in PBC patients with mild hepatic impairment (Child-Pugh A) with portal hypertension and 1.6 to 1.9-fold higher in PBC patients with moderate hepatic impairment (Child-Pugh B), compared to PBC patients with mild hepatic impairment without portal hypertension, after a single oral dose of 10 mg seladelpar.

Accumulation ratios were less than 1.2-fold in PBC patients with mild hepatic impairment with portal hypertension and PBC patients with moderate hepatic impairment following 10 mg seladelpar once daily dosing for 28 days.

Renal impairment

In a dedicated clinical study of patients with mild (eGFR ≥ 60 to < 90 mL/min), moderate (eGFR ≥ 30 to < 60 mL/min), and severe (< 30 mL/min and not on dialysis) renal impairment, the $AUC_{0\text{-}inf}$ of seladelpar was 48%, 33%, and 3% greater than in patients with normal renal function, respectively, after administration of a single 10 mg dose of seladelpar. The C_{max} of seladelpar was similar in patients with renal impairment, compared to patients with normal renal function. These differences in seladelpar $AUC_{0\text{-}inf}$ are not considered to be clinically meaningful.

The pharmacokinetics of seladelpar have not been studied in patients requiring hemodialysis.

Genetic polymorphisms

Seladelpar is mainly metabolised via the polymorphic enzyme CYP2C9. Seladelpar plasma exposures (dose-normalized $AUC_{0\text{-}inf}$) were 18% higher in CYP2C9 intermediate metabolizers (*1/*2, *1/*8, *1/*3, *2/*2, N=28) compared to CYP2C9 normal metabolizers (*1/*1, N=84) after a single dose of seladelpar (1 mg to 15 mg). No conclusions could be made for poor metabolizers, as only two subjects with *2/*3 and no subjects with *3/*3 were identified. A 47% increase in dose-normalized $AUC_{0\text{-}inf}$ was seen in the two individuals with *2/*3 compared to CYP2C9 normal metabolizers.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction and development.

Reproductive and developmental toxicity

Seladelpar had no effects on fertility or reproductive function in male and female rats at oral doses up to 100 mg/kg/day (an exposure equivalent to 223 times and 95 times the clinical exposure based on AUC of the daily recommended dose of 10 mg) in male and female rats, respectively.

In pregnant rats, seladelpar at oral doses of up to 100 mg/kg/day (an exposure equivalent to 145 times the clinical AUC) did not lead to any adverse effects on embryofetal development. In pregnant rabbits, oral doses of 40 mg/kg/day (an exposure equivalent to 41 times the clinical AUC) resulted in reduced gravid uterine weight (possibly due to maternal toxicity) and reduced fetal body weight, but no malformations or embryofoetal lethality were observed. At 10 mg/kg/day (an exposure equivalent to 2 times the clinical AUC), no adverse effects on embryofetal development were noted.
In pregnant rats, oral administration of seladelpar at doses of 0, 5, 20 or 100 mg/kg/day during gestation and lactation resulted in a dose dependent reduction in pup body weights during the pre-weaning period, which was associated with slightly reduced pre-weaning survival at 100 mg/kg/day. Growth-related delays in developmental milestones were noted (eye opening and pinna unfolding at ≥ 5 mg/kg/day; fur growth and sexual maturity at 100 mg/kg/day). Growth reductions at 100 mg/kg/day continued into the post weaning maturation period and were considered adverse events. The exposure at 100 mg/kg/day was 145-fold the clinical AUC. At 20 mg/kg/day, the dosage without negative effects on offspring, it was 15-fold the clinical AUC.

Other information

Shelf life

Do not use this medicinal product after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Keep out of reach of children.
Do not store above 30°C.

Authorisation number

70063 (Swissmedic)

Packs

Lyvdelzi 10 mg: 30 hard capsules [A]

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

Date of revision of the text

August 2025