swissmedic

Date: 3 May 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tymlos

International non-proprietary name: abaloparatide

Pharmaceutical form: powder and solvent for solution for injection in pre-filled pen

Dosage strength(s): 80 µg/40 µL

Route(s) of administration: subcutaneous

Marketing authorisation holder: Labatec Pharma SA

Marketing authorisation no.: 69246

Decision and decision date: approved on 7 March 2024

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 3
2 Background information on the procedure 4
2.1 Applicant's request(s) 4
2.2 Indication and dosage 4
2.2.1 Requested indication 4
2.2.2 Approved indication 4
2.2.3 Requested dosage 4
2.2.4 Approved dosage 4
2.3 Regulatory history (milestones) 4
3 Medical context 5
4 Quality aspects 6
4.1 Drug substance 6
4.2 Drug product 7
4.3 Quality conclusions 7
5 Nonclinical aspects 8
6 Clinical aspects 9
7 Risk management plan summary 10
8 Appendix 11

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
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
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	Food and Drug Administration (USA)
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
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
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
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)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for abaloparatide in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Treatment of osteoporosis in postmenopausal women at increased risk of fracture.

2.2.2 Approved indication

Treatment of osteoporosis in postmenopausal women at high risk of fracture (see "Pharmacological properties").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose is 80 micrograms subcutaneously once daily.
The maximum total duration of treatment with abaloparatide should not exceed 18 months.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	12 December 2022
Formal control completed	28 December 2022
List of Questions (LoQ)	25 April 2023
Response to LoQ	16 July 2023
Preliminary decision	13 October 2023
Response to preliminary decision	11 December 2023
Final decision	7 March 2024
Decision	approval

3 Medical context

Osteoporosis in postmenopausal women is a common disease characterised by reduced bone mineral density, decreased bone strength and an increased risk of fractures (most commonly of the vertebrae, distal radius, and hip). Treatment options include antiresorptive agents, such as bisphosphonates (inhibiting bone-resorbing activity of osteoclasts), as well as osteoanabolic therapies, such as with teriparatide.

4 Quality aspects

4.1 Drug substance

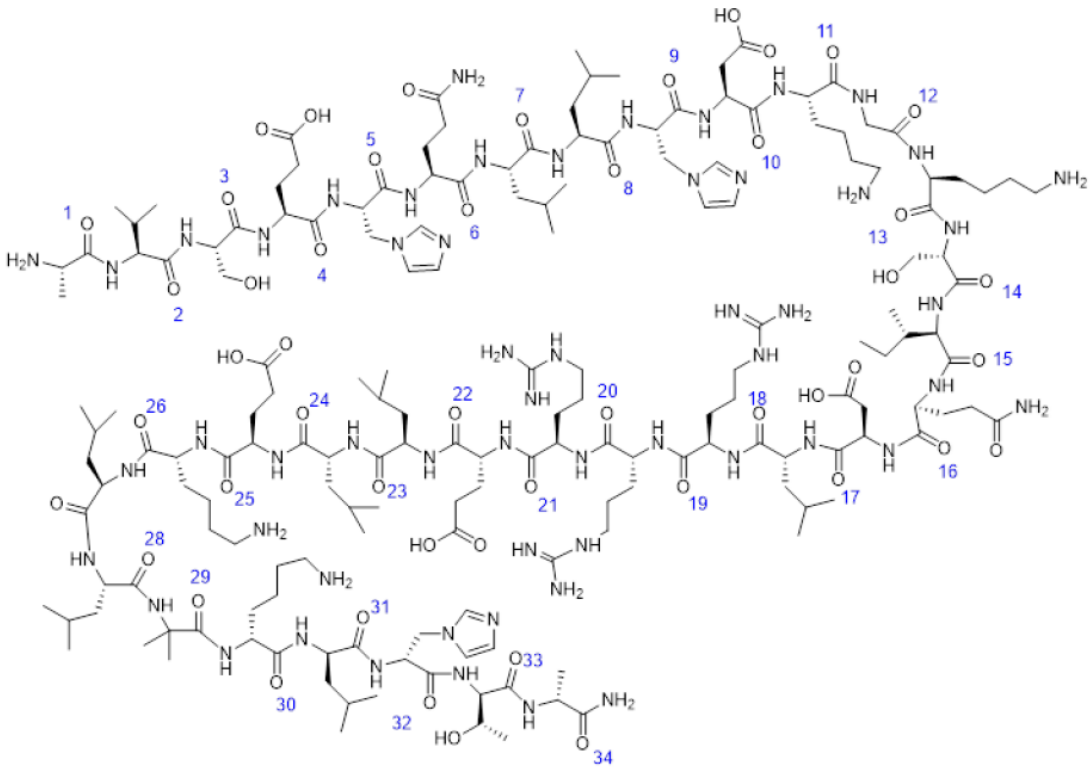
INN: Abaloparatide

Chemical name: H-Ala-Val-Ser-Glu-His-Gln-Leu-Leu-His-Asp-Lys-Gly-Lys-Ser-Ile-Gln-Asp-Leu-Arg-Arg-Arg-Glu-Leu-Leu-Glu-Lys-Leu-Leu-Aib-Lys-Leu-His-Thr-Ala-NH_2

Molecular formula: $C_{174}H_{300}N_{56}O_{49}$

Molecular mass: 3961 g × mol^{-1}

Molecular structure:



Physico-chemical properties: amorphous white to off-white powder, hygroscopic. Freely soluble in 0.1 N AcOH in water; soluble in MeOH; practically insoluble in acetone, ACN, EtOH, and THF.

Synthesis: The drug substance is obtained by adopting solid phase peptide synthesis starting from Rink amide MBHA resin. After coupling the amino acid derivatives to the resin, the crude peptide is cleaved from the solid support and deprotected, purified and desalted by preparative HPLC, and isolated by evaporation, filtration, and lyophilisation.

Specification: In order to ensure a consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability: Appropriate stability data have been presented. Based on the results, a satisfactory re-test period has been established when stored below –20 °C in HDPE bottles closed by a PP screw cap.

4.2 Drug product

Description and composition: Tymlos drug product is a sterile solution for the subcutaneous administration of abaloparatide using a multi-dose, fixed dose (80 µg), disposable pen injection system. In addition to abaloparatide, the aqueous solution contains phenol as a preservative and an acetate buffer for pH control. The fill volume is minimum 1.5 mL per cartridge.

Pharmaceutical development: Compatibility of the drug substance with the excipients was demonstrated. An optimum pH range was determined and the choice of excipients, including the preservative, has been justified. The efficacy of the antimicrobial preservative was shown. The manufacturing process development is described and the choice of sterilisation method has been justified.

Manufacture: The drug product solution is manufactured by preparation of the excipient solution and compounding of the drug substance. The aseptic filling of the cartridge is achieved by several filtration steps (bioburden reduction filtration and final sterile filtration) followed by 100 % visual inspection. Afterwards, the pens are assembled, also monitored by 100 % sensor check.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include relevant physico-chemical characteristics, identification of the drug substance, assay and purity tests, as well as sterility and bacterial endotoxin tests.

Container closure system: The container closure system for Tymlos consists of a glass cartridge fitted with an aluminium crimp cap on one end and a grey rubber plunger on the other end; the filled glass cartridge is permanently fitted into a pen assembly. The crimp cap contains a septum which is in contact with the drug solution. The materials in contact with the drug solution comply with Ph. Eur. and are considered suitable for the storage of sterile drug product solutions. The pen is a disposable administration device intended for the subcutaneous injection of multiple doses. It is a “dial and push” type fixed-dose (80 µg) pen-injector. The pen-injector and the drug product form a single integral product, intended exclusively for use in combination.

Stability: Adequate stability data have been generated according to the relevant international guidelines, including in-use stability testing. The storage recommendation is to “*store the pen in the refrigerator (between 2 °C and 8 °C) before first use. Do not freeze. After first use or after removal from the refrigerator, store the pen at a temperature not exceeding 25 °C. It should be used within 30 days.*”

4.3 Quality conclusions

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

5 Nonclinical aspects

Regarding the marketing authorisation application for Tymlos (abaloparatide), the Nonclinical Assessment Division conducted an abridged evaluation based on the published assessment report issued by the EMA (EMA/857958/2022, dated 13 October 2022).

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Tymlos in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Safety issues that are of concern for human use were identified in the nonclinical studies. The Nonclinical Safety Specifications in the RMP adequately address these nonclinical findings and their relevance for clinical use. All nonclinical data that are relevant for safety are mentioned in the information for healthcare professionals, which however needs some minor revisions.

There is no safety concern regarding impurities and excipients.

According to the ERA, the risk of abaloparatide to the environment is assumed to be low.

In conclusion, from the nonclinical point of view, approval can be supported.

6 Clinical aspects

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

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see section 8 of this report.

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 Tymlos 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 adverse reactions. See section “Undesirable effects” for how to report adverse reactions.

TYMLOS®

Composition

Active substance

Abaloparatide.

Excipients

Phenol, water for injections, sodium acetate trihydrate (for pH adjustment 0,9 mg of sodium per ml), acetic acid (for pH adjustment).

Pharmaceutical form and quantity of active substance per unit

Solution for injection in a pre-filled pen for sub-cutaneous injection. Clear and colourless solution.
Each pre-filled pen contains 3 mg of abaloparatide in 1,5 ml of solution (corresponding to 2 milligrams per ml).
Each dose (40 microliters) contains 80 micrograms of abaloparatide.

Therapeutic indications

Treatment of osteoporosis in postmenopausal women at high risk of fracture (see “Pharmacological properties”).

Posology/method of administration

Usual posology

Treatment should be carried out only by a doctor experienced in the treatment of osteoporosis.
The recommended dose is 80 micrograms for subcutaneous administration once a day.
The maximum total duration of treatment with abaloparatide should not exceed 18 months (see “Special warnings and precautions for use”).
Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.
Following cessation of abaloparatide therapy, patients may be continued on other osteoporosis therapies such as bisphosphonates.

Special populations

Hepatic impairment

No data are available in patients with impaired hepatic function. Dose adjustment is not required for these patients, as it is unlikely that hepatic impairment will have a significant effect on abaloparatide exposure.

Renal impairment

Abaloparatide must not be used in patients with severe renal impairment, including patients with end-stage renal disease. In patients with mild to moderate renal impairment, dose-based adjustment is not required.

Elderly patients

Dose adjustment based on age is not required.

Children and adolescents

Safety and efficacy of Tymlos in children and adolescents under the age of 18 have not been established. Abaloparatide should not be used in children and adolescents less than 18 years because of safety concerns (see “Contraindications”).

Missed dose

If a patient forgets or cannot administer their dose at the usual time, it can be injected within 12 hours of the normally scheduled time. Patients should not administer more than one injection in the same day and should not try to make up for a missed dose.

Method of administration

For subcutaneous use only.

The first injection(s) administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional. Patients and/or caregivers should be trained in the subcutaneous administration of abaloparatide. Detailed instructions for use is included in each pack to instruct patients on the correct use of the injection pen.

Abaloparatide should be injected in the lower abdomen. The site of the injection should be rotated every day. Injections should be administered at approximately the same time every day.

Contraindications

- Pregnancy and breast-feeding
- Women of childbearing potential
- Pre-existing hypercalcaemia

- Severe renal impairment
- Unexplained elevations of serum alkaline phosphatase
- Patients with known risks for osteosarcoma such as those who have received prior external beam or implant radiation therapy involving the skeleton
- Patients with skeletal malignancies or bone metastases
- Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”, “Excipients”
- Children and adolescents under the age of 18 (see “Posology/Method of administration”).

Special warnings and precautions for use

Orthostatic hypotension and increased heart rate

Orthostatic hypotension and transient episodes of increase in heart rate may occur with abaloparatide, typically within 4 hours of injection. Symptoms may include dizziness, palpitations, tachycardia, or nausea, and may resolve by having the patient lie down. The first injection(s) of abaloparatide should be performed under the guidance of an appropriately qualified health care professional who may observe the patient during the first hour after injection. Abaloparatide should always be administered where the patient can sit or lie down if necessary.

Abaloparatide may have vasodilating effect on vascular smooth muscle and positive chronotropic/inotropic effects on cardiac muscle. Individual benefit risk assessment is important. Blood pressure, cardiac status and ECG should be assessed prior to beginning treatment with abaloparatide. Patients with cardiac disease should be monitored for worsening of their disease. If severe orthostatic hypotension or severe cardiovascular symptoms occur, the treatment should be discontinued.

Hypercalcaemia

In normocalcaemic patients, transient elevations of serum calcium concentrations have been observed following abaloparatide injection. Serum calcium concentrations reach a maximum at approximately 4 hours and return to baseline by 24 hours after each dose. Therefore, if blood samples for serum calcium measurements are taken, this should be done approximately 24 hours after the most recent injection. Routine calcium monitoring during therapy is not required in patients without additional risk factors for hypercalcaemia.

Hypercalciuria and urolithiasis

Abaloparatide may cause hypercalciuria. It is unknown whether abaloparatide may exacerbate urolithiasis in patients with active or a history of urolithiasis. If active urolithiasis or pre-existing hypercalciuria is suspected, measurement of urinary calcium excretion should be considered.

Osteosarcoma risk

The maximum total duration of treatment with abaloparatide should be 18 months. Studies in rats indicate an increased incidence of osteosarcoma with long-term administration of abaloparatide. The use of abaloparatide should be avoided for patients at increased risk of osteosarcoma (see "Contraindications" and "Preclinical safety data").

Excipients

Tymlos contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

Interactions

No dedicated clinical drug-drug interaction studies have been performed with abaloparatide. The interaction potential of abaloparatide is regarded low considering its pharmacokinetic properties. There is no data on efficacy of abaloparatide in patients with prior or concomitant bisphosphonate or glucocorticoid treatment.

Concomitant use of vasoactive medicinal products may predispose to orthostatic hypotension since the blood pressure lowering effect of abaloparatide may be increased.

Sporadic case reports have suggested that hypercalcaemia may predispose patients to digitalis toxicity. Because abaloparatide has been shown to increase serum calcium, it should be used with caution in patients taking digitalis.

Fertility, pregnancy and lactation

This medicine is not indicated in women of childbearing potential. It is not to be used in women who are, or may be, pregnant or breast-feeding (see "Contraindications").

Pregnancy

There are no human data on the use of Tymlos in pregnant women to inform of the risks associated with the drug. Animal reproduction studies with abaloparatide have not been conducted. Tymlos is contraindicated during pregnancy.

Breast-feeding

It is unknown whether abaloparatide is excreted in human milk. A risk to the newborns/infants cannot be excluded. Tymlos is contraindicated during breast-feeding.

Fertility

No data are available on the effect of abaloparatide on human fertility. Studies in rats with abaloparatide have shown no effects on male fertility.

Effects on ability to drive and use machines

Abaloparatide has no or negligible influence on the ability to drive and use machines. Transient orthostatic hypotension or dizziness may occur following administration of abaloparatide. These patients should refrain from driving or the use of machines until symptoms have subsided.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions in patients treated with abaloparatide in the ACTIVE study were hypercalciuria (15,6%), dizziness (11,1%), back pain (8,6%), nausea (8,5%), headache (8,5%), arthralgia (8,4%), hypertension (6,8%), injection site reaction (6,2%), and palpitations (5,6%).

List of adverse reactions

Of patients in the abaloparatide ACTIVE study, 90,3% of the abaloparatide patients and 88,4% of the placebo patients reported at least 1 adverse event.

The adverse reactions associated with the use of abaloparatide in osteoporosis in the ACTIVE study and in postmarketing exposure are summarised below. The following MedDRA convention has been used for the classification of the adverse reactions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), and frequency not known (cannot be estimated from the available data).

Immune system disorders

Uncommon: Hypersensitivity

Frequency not known: Anaphylactic reaction

Metabolism and nutrition disorders

Common: Hypercalcaemia, hyperuricaemia

Psychiatric disorders

Common: Insomnia

Nervous system disorders
Very common: Dizziness
Common: Headache

Cardiac disorders
Common: Palpitations, tachycardia

Vascular disorders
Common: Hypertension
Uncommon: Orthostatic hypotension

Gastrointestinal disorders
Common: Nausea, abdominal pain, constipation, diarrhoea, vomiting
Uncommon: Abdominal distension

Skin and subcutaneous tissue disorders
Common: Pruritus, rash

Musculoskeletal and connective tissue disorders
Common: Back pain, arthralgia, pain in extremity, muscle spasms (back and legs), bone pain

Renal and urinary disorders
Very common: Hypercalciuria
Common: Nephrolithiasis

General disorders and administration site conditions
Common: Injection site reaction, fatigue, asthenia, malaise
Uncommon: Pain

Description of selected adverse reactions
Increased heart rate
In the QT study, the placebo-adjusted mean heart rate increase was 14,5 beats per minute (bpm) 15 minutes after administration. This increase in heart rate was most prominent during the first hour post dose but was seen up to 6 hours in some subjects.

In the ACTIVE study, heart rate was measured one hour post dose of every study visit, with

median heart rate increase from pre-dose of 14 bpm in abaloparatide treated patients as compared to 7 bpm in placebo treated patients. Patients with >20 bpm increase in heart rate at 1 hour after the first dose were more likely to experience palpitations and/or increases in heart rate >20 bpm during subsequent treatment. Adverse reactions of tachycardia and sinus tachycardia were reported in 1,6% of patients receiving abaloparatide and 0,4% of patients in the placebo group.

Orthostatic hypotension
In women with postmenopausal osteoporosis, adverse reactions of orthostatic hypotension were reported in 1% of patients receiving abaloparatide and 0,6% of patients in the placebo group.

Injection site reactions
Abaloparatide can cause injection site reactions including: injection site bruising, erythema, haemorrhage, hypersensitivity, pain, rash, and swelling. The overall incidence in the abaloparatide arm was 5,3% compared to 4% in the placebo group.

Laboratory findings
Serum calcium
Abaloparatide can cause transient increases in serum calcium levels measured 4 hours post-dose. The overall incidence of hypercalcaemia, defined as albumin-corrected serum calcium ≥ 2,67 mmol/L (or ≥ 10,7 mg/dL) in the abaloparatide arm was higher (3,3%) compared to the placebo group (0,4%).

Serum uric acid
Abaloparatide increased serum uric acid concentrations. In the ACTIVE study, 25% of patients in the abaloparatide group had normal baseline uric acid concentrations which were increased above the normal range at post-baseline, compared with 5% in the placebo group.

Hypercalciuria and urolithiasis
In the clinical trial of women with postmenopausal osteoporosis, the overall incidence of urine calcium/creatinine ratio > 0,00113 mmol/µmol (or > 400 mg/g) was higher with abaloparatide than with placebo (20% vs 15%, respectively). Urolithiasis was reported in 1,4% of abaloparatide-treated patients and 1,2% of placebo-treated patients.

Immunogenicity

Of the patients receiving abaloparatide for 18 months, 42,9% developed anti-abaloparatide antibodies and 28,5% developed *in vitro* neutralising antibodies. Formation of anti-abaloparatide antibodies is associated with increased clearance of abaloparatide. These changes in clearance could be related to anti-abaloparatide antibodies interfering with the accurate measurement of abaloparatide plasma concentrations. Compared to antibody negative patients, no clinically relevant differences in safety or efficacy were observed for patients who were antibody positive or who were positive for *in vitro* neutralising antibodies.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any new or serious side effects via the online portal ElViS (Electronic Vigilance System). More information is available at www.swissmedic.ch.

Overdose

Signs and symptoms

In clinical trials, abaloparatide has been administered subcutaneously in single doses of up to 320 micrograms and in repeated doses of up to 120 micrograms/day for 7 days. The primary dose-limiting adverse effect was postural dizziness.

The effects of overdose that might be expected include transient hypecalciuria, hypercalcaemia, nausea, vomiting, dizziness, palpitations, orthostatic hypotension and headache.

In the clinical programme with an earlier pen design, accidental overdose was reported in a patient who received 400 micrograms in one day (5 times the recommended clinical dose). The patient experienced asthenia, headache, nausea, and vertigo. Serum calcium was not assessed on the day of the overdose, but on the following day the patient's serum calcium was within the normal range.

Overdose management

There is no specific antidote for abaloparatide. Treatment of suspected overdose may include transitory discontinuation of treatment, monitoring of serum calcium and implementation of appropriate supportive measures, such as hydration.

Pharmacological properties

ATC code

H05AA04 (calcium homeostasis, parathyroid hormones and analogues).

Mechanism of action / Pharmacodynamic properties

Abaloparatide is a 34 amino acid peptide that shares 41% homology to parathyroid hormone

[PTH(1-34)] and 76% homology to parathyroid hormone related peptide [PTHrP(1-34)], and is an activator of the PTH1 receptor signalling pathway. Abaloparatide stimulates new bone formation on trabecular and cortical bone surfaces by stimulation of osteoblastic activity.
Abaloparatide causes transient and limited increases in bone resorption and increases bone density.

Cardiac electrophysiology
An extensive 4-way crossover QT/QTc study was conducted in 55 healthy subjects who received single doses of placebo, subcutaneous doses of abaloparatide 80 mcg and 240 mcg (three times the recommended dose) and 400 mg oral moxifloxacin. Abaloparatide increased heart rate, with a mean peak increase of 15 beats per minute (bpm) and 20 bpm at the first time point (15 minutes) after administration of 80 mcg and 240 mcg, respectively. Abaloparatide had no clinically significant effects on QTcI (individually corrected QT interval) or cardiac electrophysiology.

Clinical efficacy
The efficacy and safety of once daily abaloparatide was evaluated in a randomised, multicentre, double- blind, placebo- and open-label active comparator-controlled (teriparatide) clinical study (ACTIVE study) for 18 months of treatment with 1 month follow-up in 2070 postmenopausal women aged 50 to 86 years (mean age of 69; 15% were <65 years of age, 65% were 65 to <75 years of age, and 20% were ≥75 years of age) who were enrolled and randomised to receive abaloparatide 80 micrograms (N=696), placebo (N=688), or 20 micrograms teriparatide (N=686). Approximately 76% of patients were Caucasian, 19% were Asian, and 4% were Black. Women took daily supplemental calcium (500 to 1 000 mg) and vitamin D (400 to 800 IU) per day. The primary endpoint in ACTIVE was the incidence of new vertebral fractures in abaloparatide-treated patients versus placebo.

At baseline, the mean T-scores were -2.9 at the lumbar spine, -2.2 at the femoral neck, and -1.9 at the total hip. At baseline, 42% of patients had no prior fracture, 23% of patients had at least one prevalent vertebral fracture, and 43% had at least one prior non-vertebral fracture.

Effect on new vertebral fractures
In the ACTIVE study at 18 months, abaloparatide and teriparatide significantly reduced the absolute risk of new vertebral fractures versus placebo in postmenopausal patients with osteoporosis (p<0,0001; see Table 1).

Table 1 – ACTIVE Trial: the effect* of abaloparatide on the risk of new vertebral fracture at 18 months

Parameter	PBO (N=600)	ABL (N=583)	TER (N=600)
Number of women with vertebral fracture, n (%)	25 (4,2)	3 (0,5)	4 (0,7)
Absolute risk difference vs placebo† (%) (95% CI)	n/a	3,7 (2,0, 5,6)	3,5 (1,8, 5,5)
p-value	n/a	< 0,0001	< 0,0001

*Based on Modified Intent to Treat Population (patients with baseline and post-baseline spine radiographs).

†Absolute risk difference was calculated as (PBO – ABL) and (PBO – TER).

PBO=placebo, ABL=abaloparatide, TER=teriparatide, CI=confidence interval

Effect on non-vertebral fractures

In the ACTIVE study at 19 months, the incidence of non-vertebral fractures was similar between the abaloparatide (2,7%) and teriparatide (2,0%) groups, and not statistically different compared to placebo (3,6%) (see Table 2).

Table 2 – ACTIVE Trial: time-to-event of non-vertebral fracture at 19 months

Parameter	PBO (N=688)	ABL (N=696)	TER (N=686)
K-M estimated event rate (%) (95% CI)	3,6 (2,3 - 5,4)	2,7 (1,6 - 4,4)	2,0 (1,1 - 3,4)
Number of patients with event n (%)	21 (3,1)	15 (2,2)	12 (1,7)
Absolute risk difference vs placebo* (%) (95% CI)	n/a	0,9 (-1,1 - 2.9)	1,6 (-0,3 - 3,5)
p-value	n/a	0,0489	0,4383

*Absolute risk difference was calculated as (PBO – ABL) and (PBO – TER).

PBO=placebo, ABL= abaloparatide, TER=teriparatide, K-M=Kaplan Meier, CI=confidence interval

Effect on bone mineral density (BMD)

In the ACTIVE study, abaloparatide significantly increased BMD at all anatomical sites (lumbar spine, total hip and femoral neck) measured, versus placebo at 6, 12 and 18 months. The mean percent change in BMD at 18 months was 9,1% vs 0,5% at the lumbar spine, 3,3% vs 0% at the total hip, and 2,7% vs -0,4% at the femoral neck for abaloparatide versus placebo groups (all p < 0,0001).

Abaloparatide demonstrated consistent increases in BMD measurements regardless of age, years since menopause, race, geographic region, presence or absence of prior fracture (vertebral, non-vertebral), severity of disease and BMD at baseline.

Bone turnover markers

In postmenopausal women with osteoporosis, the bone anabolic marker (s-PINP) showed a 90% increase above baseline at 1 month, and this effect was sustained throughout the abaloparatide treatment period. The bone resorption marker (s-CTX) showed no increase at 1 month, and a transient 22% increase above baseline at 3 months that returned to baseline at the end of treatment.

Post treatment management

Extension study

Upon completion of the ACTIVE trial, 963 patients, enrolled in the ACTIVExtend trial, an open-label extension study, where all patients received up to 24 months of treatment with 70 mg alendronate (ALN) weekly and calcium and vitamin D supplements. This included 494 patients who had previously received placebo and 469 patients who had previously received abaloparatide. Patients who received teriparatide during the ACTIVE trial were not eligible to participate in the ACTIVExtend trial. Results for vertebral fracture risk reduction at 43 months since randomisation are presented in Table 3.

Effect on new vertebral fractures – Extension study

In the ACTIVExtend study at 43 months, abaloparatide/ALN significantly reduced the absolute risk of new vertebral fractures vs placebo/ALN ($p < 0,0001$; see Table 3). Teriparatide followed by alendronate has not been studied.

Table 3 – ACTIVE trial: the effect* of abaloparatide/ALN on the risk of new vertebral fracture at 43 months†

Parameter	**PBO/ALN (N=489)**	**ABL/ALN (N=457)**
Number of women with vertebral fracture, n (%)	26 (5,3)	54 (0,9)
Absolute risk difference vs placebo‡ (%) (95% CI)	n/a	4,4 (2,3 - 6,9)
p-value	n/a	< 0,0001

*Based on Modified Intent to Treat Population (patients with baseline and post-baseline spine radiographs).

†Alendronate started at 19 months

‡Absolute risk difference was calculated as (PBO / ALN – ABL / ALN).

PBO = placebo, ABL = abaloparatide, ALN=alendronate, CI=confidence interval

Effect on new non-vertebral fractures – Extension study

In the ACTIVExtend study at 43 months, abaloparatide/ALN numerically reduced the risk of non-vertebral fractures versus placebo/ALN. The incidence of non-vertebral fractures with

abaloparatide/ALN (4,2%) was not statistically different compared to placebo (6,7%) (see Table 4).

Table 4 – ACTIVExtend trial: time-to-event of non-vertebral fracture at 43 months*

Parameter	**PBO/ALN (N = 494)**	**ABL/ALN (N = 469)**
K-M estimated event rate (%) (95% CI)	6,8 (4,8 - 9,3)	4,2 (2,7 - 6,4)
Number of patients with event n (%)	32 (6,5)	19 (4,1)
Absolute risk difference vs placebo† (%) (95% CI)	n/a	2,5 (-0,4 - 5,4)

*Alendronate started at 19 months

† Absolute risk difference was calculated as (PBO/ALN – ABL/ALN).

PBO=placebo, ABL=abaloparatide, ALN=alendronate, K-M=Kaplan Meier, CI=confidence interval

Effect on bone mineral density (BMD) – Extension study

The mean percent change in BMD through 43 months was 14,7% vs 6,8% at the lumbar spine, 6,3% vs 2,9% at the total hip, 5,0% vs 1,6% at the femoral neck, and 1,1% vs 1,1% at the ultra-distal radius for abaloparatide/ALN versus placebo/ALN groups, respectively.

Pharmacokinetic properties

Absorption

The median (range) time to peak concentration of abaloparatide 80 micrograms was 0,5 h (0,25 to 0,52 h) following subcutaneous administration. The absolute bioavailability of abaloparatide in healthy subjects after subcutaneous administration of 80 micrograms dose was about 39%.

Distribution

The *in vitro* plasma protein binding of abaloparatide was approximately 70%. The volume of distribution was approximately 45 L.

Biotransformation

No specific metabolism or excretion studies have been performed with abaloparatide. The metabolism of abaloparatide is consistent with non-specific proteolytic degradation into smaller peptide fragments, followed by elimination by renal clearance. *In vitro* studies showed that abaloparatide, at clinically relevant concentrations, does not inhibit or induce cytochrome P450 enzymes.

Elimination

The mean apparent total plasma clearance for subcutaneous administration is 168 L/h in healthy subjects, and the mean half-life of abaloparatide is about 1 h. The peptide fragments are primarily eliminated through renal excretion. Active secretion of abaloparatide in the kidneys cannot be ruled out.

Abaloparatide is not a substrate of the renal transporters P-gp, OAT1, OAT3, OCT2, MATE1 or MATE2K. Furthermore, abaloparatide does not inhibit P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 transporters *in vitro* at its clinically relevant concentrations.

Linearity

Abaloparatide systemic exposure was generally increasing with the increase of its subcutaneous doses from 5 micrograms up to 240 micrograms. There was a general tendency towards less than dose- proportional increases, and no further increase in abaloparatide systemic exposure was observed as its dose increased to 280 micrograms and 320 micrograms.

Special populations

Renal impairment

Abaloparatide exposure increased with decreasing CrCl. Subjects with mild, moderate and severe renal impairment had C_{max} increases of 3%, 28% and 44%, respectively, and AUC increases of 17%, 68% and 113%, respectively, compared to subjects with normal renal function.

No studies have been performed in patients undergoing dialysis for chronic renal failure.

Hepatic impairment

No studies have been performed in patients with hepatic impairment. Abaloparatide is a peptide and not an inhibitor or an inducer of hepatic drug metabolising enzymes. The elimination is through proteolytic degradation and renal excretion, and it is unlikely that hepatic impairment will have any significant effect on abaloparatide exposure. No dose adjustment is needed for these patients.

Elderly

No age-related differences in abaloparatide pharmacokinetics were detected during clinical studies, including postmenopausal women ranging from 49 to 86 years of age.

Preclinical safety data

In a 2-year rat carcinogenicity study, abaloparatide displayed an increase in the overall incidence of osteosarcomas. Neoplastic changes related to the treatment with abaloparatide consisted of dose-dependent increased incidence of osteosarcomas and osteoblastomas. The incidence and earliest occurrence of tumours was similar in both male and female rats. The relevance of these

rat findings to humans is uncertain, thus the use of abaloparatide should be avoided for patients at increased risk of osteosarcoma (see “Special warnings and precautions for use”).
In toxicology studies in rats and monkeys, findings included soft tissue mineralization at doses that were approximately 2 and 3 times, respectively, the exposure in humans at daily subcutaneous doses of 80 micrograms.
Subcutaneous administration of abaloparatide to the conscious dog produced a dose-dependent transient increase in heart rate lasting approximately 3 hours, had marginal effects on mean arterial blood pressure. Additionally, abaloparatide had marginal effects on the QTc interval, with a non-significant tendency towards a decrease in QTc with increasing dose, which is consistent with its minimal effects on hERG potassium currents and Purkinje fibres at clinically relevant concentrations.
Abaloparatide was not genotoxic or mutagenic in a standard battery of tests.
No embryofoetal development or pre/postnatal development studies have been conducted in female animals because the intended population for abaloparatide is postmenopausal women.
Effects on male fertility were evaluated in rats, and no impact on male fertility was observed at doses 27 times the exposure in humans at daily subcutaneous doses of 80 micrograms.

Pharmaceutical particulars

Incompatibilities
In the absence of compatibility studies, Tymlos must not be mixed with other medicinal products.

Expiry date

Do not use this medicine after the expiry date which is stated on the carton.

Special precautions for storage

Before first use store the pen in a refrigerator (between 2 °C and 8 °C). Do not freeze.

Do not use Tymlos if it is or was frozen.

After first use or once removed from the refrigerator, store the pen below 25 °C. It must be used within 30 days.
Keep in the outer carton and out of reach of children.
Special precautions for disposal and other handling

Each pen should be used by only one patient. A new, sterile needle must be used for every injection. The pen should only be used with 8 mm, 31-gauge needles. No needles are supplied with the medicinal product. Do not store the pen with the needle attached.

Tymlos should not be used if the solution is cloudy, coloured or contains particles.

Before using the pen device for the first time, the patient should read and understand the instructions on how to use the pen. A detailed Instructions for Use is provided with the pen in the carton.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Marketing authorisation number

69246 (Swissmedic)

Nature and contents of container

Cartridge (siliconised Type I glass) with a plunger (chlorobutyl rubber), crimp cap (bromobutyl rubber seal)/aluminium assembled into a disposable pen.

Each pre-filled pen contains 1,5 mL of solution (30 doses).

Pack size of 1 pre-filled pen.[B]

Marketing authorisation holder

Labatec Pharma SA, 1217 Meyrin (Genève)

Date of revision of the text

October 2023