European Union Risk Management Plan for Bilprevda (Denosumab 120 mg)

RMP version to be assessed as part of this application:

RMP Version number: 2.0

Data lock point for this RMP: 31Mar2026

Date of final sign-off: 10Jun2026

Rationale for submitting an updated RMP:

- To align with the reference medicinal product denosumab (Trade name: Xgeva®) updated EU RMP V37.1.
- To remove the following safety concerns:
  - important identified risk of 'Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons'
  - important potential risks of 'Malignancy' and 'Delay in diagnosis of primary malignancy in giant cell tumor of bone'
  - missing information of 'Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone'

Summary of significant changes in this RMP:

Part/Module/Annex	Major Change(s)	Version and Date
Part I: Product Overview	As this is the first EU RMP update following EC approval, the proposed indications, dosage in the EEA, pharmaceutical form and strengths were moved from 'proposed' to 'current'.	2.0, 09Jun2026
Part II: SV Post-authorization experience	Added the post marketing exposure data up to a data lock point of 31Mar2026.	2.0, 09Jun2026
Part II: SVII Identified and potential risks	Removed safety risks from the initial Bilprevda EU RMP version.	2.0, 09Jun2026

Part/Module/Annex	Major Change(s)	Version and Date
	Removed the following safety concerns with justification: • important identified risk of 'Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons' • important potential risks of 'Malignancy' and 'Delay in diagnosis of primary malignancy in giant cell tumor of bone' • missing information of 'Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone'. Added data from the completed studies with reference denosumab product for osteonecrosis of the jaw and atypical femoral fracture.	
Part II: SVIII Summary of safety concerns	Updated safety concerns per changes listed above.	2.0, 09Jun2026
Part V	Updated safety concerns per changes listed above.	2.0, 09Jun2026
Part VI	Updated safety concerns per changes listed above.	2.0, 09Jun2026
Part VII: Annexes	Updated Annex 4 - Targeted Follow-up Questionnaires to V2.0 (added new MAH logo following the marketing authorization transfer).	2.0, 09Jun2026

Other RMP versions under evaluation: No RMP versions are currently under evaluation.

QPPV name: Carmen Arques

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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Abbreviations

Term/Abbreviation	Explanation
AAOMS	American Association of Oral and Maxillofacial Surgeons
AFF	Atypical femoral fracture
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMD	Bone Mineral Density
CG formula	Cockcroft-Gault formula
CI	Confidence Interval
CN	China
COX-2	Cyclooxygenase-2
CRPC	Castrate-Resistant Prostate Cancer
CV	Cardiovascular
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUR	Europe
GCTB	Giant Cell Tumour of Bone
GLP-1	Glucagon-Like Peptide-1
HALT	Hormone Ablation Therapy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IgG2	Immunoglobulin G2
INN	International Nonproprietary Name
IV	Intravenous or Intravenously
MAH	Marketing Authorization Holder
NPM	New Primary Malignancy
ONJ	Osteonecrosis of the Jaw
OPG	Osteoprotegerin

Term/Abbreviation	Explanation
PI	Product Information
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PMGCTB	Primary Malignancy in Giant Cell Tumour of Bone
PMO	Postmenopausal Osteoporosis
PSUR	Periodic Safety Update Report
PY	Person-Year of follow-up
Q4W	Every 4 Weeks
RA	Rheumatoid Arthritis
RANK	Receptor Activator of Nuclear Factor Kappa-B
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
RMP	Risk Management Plan
SC	Subcutaneous
SGLT	Sodium-Glucose Cotransporter-2
SmPC	Summary of Product Characteristics
SRE	Skeletal Related Event
ULN	Upper Limit Normal
US	United States

Part I: Product Overview

Table 1 Product Overview

Active substance (International Nonproprietary Name [INN] or common name)	Denosumab
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	M05BX04
Marketing Authorisation Applicant or Marketing Authorization Holder (MAH)	SciencePharma Sp. z o. o.
Medicinal products to which this Risk Management Plan (RMP) refers	1 Bilprevda 120 mg solution for injection in vial
Invented name in the European Economic Area (EEA)	Bilprevda
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Recombinant Anti-RANKL fully human monoclonal IgG2 antibody
	Summary of mode of action: Bilprevda is a fully human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancer-induced bone destruction.
	Important information about its composition: Bilprevda is a biosimilar to Denosumab (Xgeva®).
Hyperlink to the Product Information	Link to Bilprevda Product Information (PI) on EMA website: https://www.ema.europa.eu/en/medicines/human/EPAR/bilprevda
Indications in the EEA	Current: • Prevention of skeletal related events (SREs) (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone. • Treatment of adults and skeletally mature adolescents with Giant cell tumours of bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity.

	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: Prevention of SREs in adults with advanced malignancies involving bone: - The recommended dose of Bilprevda is 120 mg administered as a single subcutaneous (SC) injection once every 4 weeks (Q4W) into the thigh, abdomen or upper arm. Treatment of GCTB: - The recommended dose of Bilprevda is 120 mg administered as a single SC injection Q4W into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy. Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strength(s)	Current (if applicable): 120 mg/1.7 mL solution for SC injection
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

HLX14 is being developed as a biosimilar product to the reference medicinal product denosumab (Trade name: Xgeva®). This section is not applicable for biosimilar products.

Part II: Module SII - Non-clinical part of the safety specification

As a biosimilar, the non-clinical development of HLX14 has primarily focussed on the in vitro comparison of HLX14 to Xgeva® for biosimilarity.

Based on the outcome of the analytical similarity exercise and in vitro functional/biological assays, the similarity between HLX14 (120 mg, vial) and Xgeva® has been established. As such, the non-clinical data generated for Xgeva® can be referenced for HLX14, and there are no additional non-clinical safety findings which could constitute an important potential risk to the target population.

In conclusion, there are no additional safety concerns, as a result of non-clinical studies, that require inclusion in the RMP for HLX14.

Part II: Module SIII - Clinical trial exposure

As HLX14 is a biosimilar, safety data collected from studies conducted with denosumab licenced in the European Union (EU) as Xgeva® provide the main data used to support a safety assessment of HLX14. Thus, the data in the summary of product characteristics (SmPC) of Xgeva® provides the basis of the known safety profile for denosumab.

The clinical development program for HLX14 (denosumab biosimilar) consisted of one Phase I pharmacokinetic (PK) study (HLX14-001) conducted in Chinese healthy adult male volunteers, and one Phase III study (HLX14-002-PMOP301) conducted in postmenopausal female patients with osteoporosis at high risk of fracture.

The pooled safety data set includes the safety data in above two clinical trials with HLX14 (HLX14-001, HLX14-002-PMOP301). **Table 2** provides the overview of the clinical trials of HLX14 pooled in safety evaluations. The cumulative subject exposure to HLX14 and Prolia® was provided in **Table 3-1** and **Table 3-2**. Further details on cumulative subject exposure categorized by age, gender, dose and ethnic origin are provided in **Table 4**, **Table 5** and **Table 6** respectively.

Table 2 Overview of Two Clinical Trials of HLX14 Pooled in Safety Evaluations

Protocol Number	Study Objectives	Subjects	Treatments Administered	Study Endpoints
HLX14-001 Phase I	Primary objective: *Part I of the Study* To compare the PK parameters of HLX14 and EU-Prolia® (denosumab) in healthy adult male subjects to further provide basis for the study design of part II. *Part II of the Study* To compare the PK similarity of HLX14 and Prolia® (US, EU, and CN-sourced denosumab) in healthy adult male subjects.	Part I of the Study: A total of 24 healthy male subjects were planned to be enrolled, with 12 subjects in each group. The actual number of enrolled subjects was consistent with the planned number of enrollments, and a total of 24 subjects were actually enrolled, with 12 subjects in each group. Part II of the Study: A total of 228 healthy male subjects were planned to be enrolled, with 57 subjects in each group. A total of 228 healthy male subjects were actually enrolled, with 58 subjects in the HLX14 group, 57 subjects in the US-Prolia® group, 56 subjects in the EU-Prolia® group, and 57 subjects in the CN-Prolia® group.	Single dose of HLX14 (60 mg/mL) or EU-Prolia® (60 mg/mL) Single dose of HLX14 (60 mg/mL) or US, EU, or CN-sourced Prolia® (60 mg/mL)	Primary endpoints: • Area under the serum drug concentration-time curve from time 0 to the last concentration-quantifiable time t (AUC_{0-t}); • Maximum serum drug concentration (C_{max}); • Area under the serum drug concentration-time curve from time 0 to infinity (inf) (AUC_{0-inf}).
HLX14-002-PMOP301 Phase III	Primary objective: To assess the equivalence of the primary clinical efficacy endpoint and primary PD endpoint between HLX14 and comparator Prolia® in postmenopausal women with osteoporosis at high risk of fracture.	A total of 478 postmenopausal women with osteoporosis at high risk of fracture were planned to be enrolled, with 239 subjects in each group. A total of 514 postmenopausal women with osteoporosis at high risk of fracture were actually enrolled, with 256 subjects in the HLX14 group and 258 subjects in the Prolia® group.	A total of 2 doses of HLX14 or denosumab (Prolia®) (60 mg/mL, once every 6 months)	Primary endpoints: • Percent change from baseline in BMD at the lumbar spine to Week 52 (D365). Note: the percent change in BMD was calculated as: (test value - baseline value)/ (baseline value) × 100% • Area under the effect-time curve for percent change from baseline of serum type I collagen C-telopeptide (s-CTX) from 0 to Week 26 (D183) ($AUEC_{0-26W}$).

Table 3-1 Summary of Drug Exposure

	HLX14-001		HLX14-002-PMOP301	
	HLX14 (N=70)	Prolia® (N=182)	HLX14 (N=256)	Prolia® (N=258)
Total exposure days, (days)				
n	70	182	256	258
Mean (SD)	1.0 (0)	1.0 (0)	169.1 (52.24)	170.9 (51.09)
Median (Min, Max)	1.0 (1, 1)	1.0 (1, 1)	184.0 (1, 230)	184.0 (1, 232)

Table 3-2 Duration of Exposure

	HLX14		Prolia®	
Duration of exposure	Number of subjects	Person time (months)	Number of subjects	Person time (months)
Indication - NA (HLX14-001)				
1 day	70	2.30	182	5.98
Total	70	2.30	182	5.98
Indication - postmenopausal osteoporosis (PMO)				
1 day	22	0.72	21	0.69
>1 day	234	1421.67	237	1448.31
Total	256	1422.39	258	1449.00

Table 4 Age group and gender

	HLX14		Prolia®	
	Number of subjects	Person time (months)	Number of subjects	Person time (months)
Indication - NA (HLX14-001)				
Age group				
<18	0	0	0	0
18-64	70	2.30	182	5.98
≥65	0	0	0	0
Male	70	2.30	182	5.98
Female	0	0	0	0
Total	70	2.30	182	5.98
Indication - PMO				
Age group				
<18	0	0	0	0
18-64	81	470.97	83	481.25
≥65	175	951.43	175	967.75
Male	0	0	0	0
Female	256	1422.39	258	1449.00
Total	256	1422.39	258	1449.00

Table 5 Dose

	HLX14		Prolia®	
Duration of exposure	Number of subjects	Person time (months)	Number of subjects	Person time (months)
Indication - NA (HLX14-001)				
60 mg	70	2.30	182	5.98
Total	70	2.30	182	5.98
Indication - PMO				
60 mg	22	0.72	21	0.69
120 mg	234	1421.67	237	1448.31
Total	256	1422.39	258	1449.00

Table 6 Ethnic origin

	HLX14		Prolia®	
Ethnic Origin	Number of subjects	Person time (months)	Number of subjects	Person time (months)
Indication - NA (HLX14-001)				
Asian	70	2.30	182	5.98
White	0	0	0	0
Total	70	2.30	182	5.98
Indication - PMO				
Asian	255	1419.47	257	1442.99
White	1	2.92	1	6.01
Total	256	1422.39	258	1449.00

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

In accordance with the guideline on similar biological medicinal products (CHMP/437/04 Rev1), extrapolation of clinical safety and efficacy data to other indications of the originator product that are not specifically studied during the clinical trial development is possible based on the totality of the evidence and appropriate clinical justification. The mechanism of action of denosumab is identical across the different indications, both primary and secondary osteoporosis as well as local bone affection around metastases. Consequently, extrapolation to all therapeutic indications of Prolia® and Xgeva® approved is acceptable, provided biosimilarity has been demonstrated in a full analytical similarity exercise and clinical data demonstrate similarity in an indication representative of both efficacy and safety. Therefore, the exclusion criteria consistent with 60 mg in HLX14-002-PMOP301 study in postmenopausal women with osteoporosis at high risk of fracture below could be referred to.

Criterion 1: Diseases and medicines that may affect bone metabolism.

Reason for exclusion: Various metabolic bone diseases, such as osteomalacia or osteogenesis imperfecta; Paget's disease (Paget disease of bone); Cushing's syndrome; hyperprolactinemia; hypopituitarism; acromegaly; multiple myeloma; hyperparathyroidism or hypoparathyroidism, thyroid disorders, rheumatoid arthritis or ankylosing spondylitis, type 1 diabetic patients, or type 2 diabetic patients who have poor blood glucose control or are treated with insulin, glucagon-like peptide-1 (GLP-1), thiazolidinediones, sodium-glucose cotransporter-2 (SGLT2) inhibitors, etc. These diseases may affect bone metabolism and percent change in bone mineral density (BMD). Osteoporosis treatments, or medications that affect bone metabolism or any herbal medications, these medicines may confound the determination of efficacy, and may increase the risk for safety events, such as osteonecrosis of the jaw (ONJ) and atypical femur fractures due to significant suppression of bone remodelling.

Is it considered to be included as missing information?: No

Rationale: The efficacy of denosumab in patients with diseases and medicines that may affect bone metabolism have not been established. HLX14 is not indicated in treatment of such conditions and population.

Criterion 2: Malabsorption syndrome or various gastrointestinal disorders associated with malabsorption, Vitamin D deficiency, abnormal serum calcium.

Reason for exclusion: Subjects with Crohn's disease, chronic pancreatitis, and known malabsorption of calcium or vitamin D, may affect the absorption of calcium and vitamin D and affect bone metabolism. In the Prolia® post-marketing setting, severe symptomatic hypocalcaemia (including fatal cases) has been reported, with most cases occurring in the first weeks of initiating therapy, but it can occur later. Vitamin D deficiency and abnormal serum calcium must be corrected prior to initiating therapy with denosumab.

Is it considered to be included as missing information?: No

Rationale: Hypocalcaemia is a contraindication in the Prolia®/HLX14 SmPC

Criterion 3: Oral and dental diseases.

Reason for exclusion: Patients receiving denosumab may develop pain in the mouth and/or jaw, swelling or non-healing of sores in the mouth or jaw, discharge, numbness, or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis). While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.

Is it considered to be included as missing information?: No

Rationale: Osteonecrosis of the jaw is an important identified risk that is covered in the SmPC and RMP of Prolia®/HLX14.

Criterion 4: Subjects with a history or presence of hip fracture or prevalent vertebral fracture, subjects in active healing fracture in the opinion of the investigator, or subjects at very high risk of fracture who must be treated immediately with an active drug in the opinion of the investigator.

Reason for exclusion: To reduce inter-subject variability, it is strongly recommended to exclude the patients with prevalent vertebral or hip fracture from the study. These fractures may affect the bone turnover at screening.

Is it considered to be included as missing information?: No

Rationale: Denosumab is indicated for the treatment of bone loss and osteoporosis, recent or healing fracture may affect bone turnover at screening thus confound results. Fracture healing complications is an important potential risk covered in Prolia®/HLX14 RMP.

Criterion 5: Known allergic to the drugs listed in the study protocol, including a history of allergy to denosumab, any recombinant protein drugs, or any ingredients used in HLX14 or Prolia®.

Reason for exclusion: In the Prolia® post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving Prolia®. Patients who are hypersensitive to denosumab or to any of the excipients should not receive HLX14 or Prolia®.

Is it considered to be included as missing information?: No

Rationale: It is a contraindication in the Prolia®/HLX14 SmPC.

Criterion 6: With a history and presence of smoking, except for the following situation:

1) **Non-smokers (A history of never smoking >5 cigarettes/day and not smoking at all for at least the last 2 years prior to screening process);**

2) Light smokers (With smoking habit <5 cigarettes/day, smoking period <10 years. Light smokers should have not smoked more than 1 cigarette in the week before starting the medical screening process).

Reason for exclusion: The available literature suggests that smoking may be associated with a greater rate of bone loss, thus an impact on bone mass cannot be ruled out. Smoking may confound the determination of efficacy.

Is it considered to be included as missing information?: No

Rationale: The efficacy of denosumab in patients who are current or former smokers have not been established. The safety information will be closely monitored in post-marketing activities.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is specific to that for biosimilars and is therefore unlikely to detect certain types of adverse reactions such as rare or uncommon adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

In accordance with the guideline on similar biological medicinal products (CHMP/437/04 Rev1), extrapolation of clinical safety and efficacy data to other indications of the originator product that are not specifically studied during the clinical trial development is possible based on the totality of the evidence and appropriate clinical justification. The mechanism of action of denosumab is identical across the different indications, both primary and secondary osteoporosis as well as local bone affection around metastases. Consequently, extrapolation to all therapeutic indications of Prolia® and Xgeva® approved is acceptable, provided biosimilarity has been demonstrated in a full analytical similarity exercise and clinical data demonstrate similarity in an indication representative of both efficacy and safety. Therefore, the exclusion criteria consistent with 60 mg in HLX14-002-PMOP301 study below could be referred to.

Table 7 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	**Patients with hepatic impairment:** In HLX14-002-PMOP301 study, subjects were excluded with hepatic insufficiency: Serum aspartate aminotransferase (AST) ≥2×upper limit normal (ULN); serum alanine aminotransferase (ALT) ≥2×ULN;

• Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	bilirubin ≥1.5×ULN (when direct bilirubin is <35% total bilirubin, indirect bilirubin ≥1.5×ULN is allowed). In HLX14-001 study, subjects with clinically significant diseases were excluded. **Patients with renal impairment:** In HLX14-002-PMOP301 study, subjects were excluded with severe renal impairment due to renal disease with a glomerular filtration rate <30 mL/min (recommended to calculate as per Cockcroft–Gault (CG) formula). In HLX14-001 study, subjects with clinically significant diseases were excluded. **Patients with cardiovascular impairment:** In HLX14-002-PMOP301 study, subjects with serious primary diseases in the cardiovascular, cerebrovascular, or hematopoietic system judged by investigator were excluded from clinical trial participation. In HLX14-001 study, subjects with clinically significant diseases were excluded. **Immunocompromised patients:** In HLX14-002-PMOP301 study, no specific exclusions with exception of human immunodeficiency virus (HIV) positive. In HLX14-001 study, subjects with clinically significant diseases were excluded. **Patients with a disease severity different from inclusion criteria in clinical trials:** HLX14-002-PMOP301 is being studied in postmenopausal women with osteoporosis at high risk of fracture. The safety population may have a protocol deviation of pivotal study HLX14-002-PMOP301. A subject with the BMD T values of lumbar spine and total hip were -2.49 and -2.48 in the central imaging report was mistakenly enrolled and included in the safety set. Not included in HLX14-001 study.
Population with relevant different ethnic origin	HLX14-002-PMOP301 is being studied in Chinese and Australian postmenopausal women with osteoporosis who are at a high risk for fractures. No major differences were observed when adverse events were analysed by the subjects' racial origin. There are currently no data indicating that specific ethnic backgrounds may impact the clinical safety of HLX14. HLX14-001 was conducted in Chinese healthy adult male subjects.

Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	HLX14 has not been studied in paediatric patients in the clinical development program.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate the exposure

Postmarketing patient exposure estimates are reported overall and for the following regions in which exposure has been noted at the time of this EU RMP DLP: Europe (EUR) (Germany, Spain, the United Kingdom (UK)), and the USA. Cumulative post-marketing exposure for Bilprevda was estimated from sales data. The unit sales data for countries were obtained from Organon which is the commercial lead in these countries. The methodology used to calculate the exposure is based on Bilprevda dose required for treatment once every 4 weeks, one sold vial of product presentation was assumed to correspond to one administered dose. Method of estimation: number of patients exposed = total vials sold/estimated average vials of treatment for a single patient. Cumulatively, it was estimated that 737 patients used the product.

As indication-specific and patient's characteristics utilisation data were unavailable, therefore no stratification by indication and patient age groups and sex could be performed.

SV.1.2 Exposure

Table 8 reports the estimated cumulative number of patients exposed to Bilprevda accrued worldwide in SciencePharma Sp. z o. o. territories (the EU, the UK) and in territories where Shanghai Henlius Biotech, Inc. is the Marketing Authorisation Holder (the USA).

Table 8 Cumulative Estimated Number of Patients Exposed to Bilprevda in the Postmarketing Setting (29Aug2025 - 31Mar2026)

Region/Country	Vials Sold	Estimated average vials of treatment for a single patient in the reporting period	Estimated Exposed Number of Patients
United States	4443	7	635
EUR (Germany, Spain & UK)	715	7	102
Cumulative	5158	7	737

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

No evidence to suggest that a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and potential risks

As a biosimilar product to the reference medicinal product denosumab (Trade name: Xgeva®), the safety concerns of HLX14 are aligned with that of the reference medicinal product, no discrepancies of safety concerns were found in the clinical development.

The important identified risks of HLX14 include osteonecrosis of the jaw and atypical femoral fracture.

The important potential risks of HLX14 include cardiovascular events and hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons.

The missing information of HLX14 include use in patients with prior intravenous bisphosphonate treatment and off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Table 9 New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
Important Identified Risks		
Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons	Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons, previously classified as an important identified risk, has been removed from the list of safety concerns.	In line with the updated EU RMP V37.1 of the reference product denosumab: Hypercalcemia several months after the last dose in patients with giant cell tumor of bone and in patients with growing skeletons, is a well characterized safety concern. The long-term safety follow-up study with reference denosumab product did not provide new data concerning characterisation of this risk. There are no outstanding additional pharmacovigilance or risk minimisation activities. The current SmPC language is adequate to manage hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone and in patients with growing skeletons.
Important Potential Risks		
Malignancy	Malignancy, previously classified as an important potential risk, has been removed from the list of safety concerns.	In line with the updated EU RMP V37.1 of the reference product denosumab: With the completion of study with reference denosumab product, the cumulative evidence from clinical trials, observational studies, literature and post-marketing surveillance demonstrates that: • the incidence of malignancy with denosumab is low and consistent with expected background rates in the underlying patient populations. • no causal link between denosumab and malignancy has been established. • new primary malignancy (NPM) is already addressed in the SmPC, ensuring appropriate communication of this information.

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
		The clinical trial and observational study data indicate no excess risk of malignancy with reference denosumab product compared to zoledronic acid. There are currently no additional pharmacovigilance or risk minimization activities ongoing or planned to further characterize this risk. The current SmPC language is adequate to manage malignancy in patients with giant cell tumor of bone and in patients with growing skeletons.
Delay in diagnosis of primary malignancy in giant cell tumor of bone	Delay in diagnosis of primary malignancy in giant cell tumor of bone previously classified as an important potential risk, has been removed from the list of safety concerns.	In line with the updated EU RMP V37.1 of the reference denosumab product: The data from follow-up study with reference denosumab product, did not indicate a risk of delay in diagnosis of primary malignancy in giant cell tumor of bone with reference denosumab product. Based on the current data, no risk with denosumab was identified. There are currently no additional pharmacovigilance or risk minimization activities ongoing or planned to further characterize this risk.
Missing Information		
Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone	Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone previously classified as missing information, has been removed from the list of safety concerns.	In line with the updated EU RMP V37.1 of the reference denosumab product: The classification of 'Safety with long-term treatment and with long-term follow-up after treatment in adults and skeletally mature adolescents with giant cell tumor of bone' as missing information is no longer appropriate with the completion of follow-up study. The overall safety profile of denosumab in follow-up study was similar to the safety profile of parent open-label, multi-center phase 2 study of reference denosumab product in subjects with giant cell tumor of bone. The overall safety profile of

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
		denosumab in the completed open-label, multi-center phase 2 study of reference denosumab product in subjects with giant cell tumor of bone, was similar to the safety profile of denosumab observed in the treatment of subjects with advanced cancer and bone metastases.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Based on the EMA guide on similar biological medicinal products, the RMP should take into account identified and potential risks associated with the use of the reference product. Therefore, this section will contain all the important identified risks and important potential risks described in the European Public Assessment Report (EPAR) for the reference product, Xgeva®, and from the scientific literature.

Details of Important Identified Risk 1: Osteonecrosis of the Jaw

Potential mechanisms:

Osteonecrosis of the jaw (ONJ) appears to be multifactorial and multiple hypotheses have been postulated and have included factors such as inhibition of bone remodelling, infection and inflammation, inhibition of angiogenesis, soft tissue toxicity, altered immunity and genetic predisposition. As of yet, evidence supporting these hypotheses has been variable and little is understood in how these multiple pathways might interact.

Evidence source(s) and strength of evidence:

This risk has been reported in clinical trials, the scientific literature and is also reflected in the SmPC of the reference medicinal product. This risk was further supported by denosumab post-marketing reports.

Characterisation of the risk:

(1) Frequency: According to the clinical data of the reference medicinal product, in the pooled pivotal SRE Solid Tumour studies, the subject incidence of positively adjudicated adverse events of ONJ was 1.8% in the denosumab group and 1.3% in the zoledronic acid group; the hazard ratio (HR) was 1.38 (95% confidence interval [CI]: 0.91, 2.11). In the SRE multiple myeloma study, the subject incidence of positively adjudicated adverse events of ONJ was 4.1% in the denosumab group and 2.8% in the zoledronic acid group; the HR was 1.47 (95% CI: 0.88, 2.48).

In clinical trials, the incidence of ONJ was higher with longer duration of exposure.

In a non-interventional post-marketing observational study of 2877 patients with cancer treated with reference denosumab product or zoledronic acid for SRE prevention, the incidence rates (95% CI) of medically confirmed ONJ per 100 person-years were 3.0 (2.3, 3.7) in the denosumab inception cohort, 1.0 (0.6, 1.5) in the zoledronic acid inception cohort, and 4.3 (2.8, 6.3) in the denosumab-switch cohort (this cohort included patients who switched to denosumab after having started antiresorptive therapy with bisphosphonates for SRE prevention of no more than 2 years' net duration).

In a long-term phase 2 open-label clinical trial reference denosumab product in patients with giant cell tumor of bone, ONJ was confirmed in 6.8% of patients, including 1 adolescent (median number of 34 doses; range: 4 to 116). At the completion of the trial, median time on trial including safety follow up phase was 60.9 months (range: 0 to 112.6). The patient-year adjusted incidence of confirmed ONJ was 1.5 per 100 patient-years overall (0.2 per 100 patient-

years during the first year of treatment, 1.5 in the second year, 1.8 in the third year, 2.1 in the fourth year, 1.4 in the fifth year, and 2.2 thereafter). The median time to ONJ was 41 months (range: 11 to 96).

A continuation study was conducted to follow subjects with giant cell tumor of bone, who were treated in a long-term phase 2 open-label clinical trial reference denosumab product in patients with giant cell tumor of bone, for an additional 5 or more years. ONJ was reported in 6 patients (11.8%) of the 51 exposed patients with median total 42 doses of denosumab. Three of these cases of ONJ were medically confirmed.

In a postmarketing ONJ case registry study with reference denosumab product, a total of 148 subjects of 282 subjects (52.5%) had resolution of their ONJ at last assessment, with a median (range) time from suspected ONJ onset to resolution of 10.10 months (0.03 to 64.74 months) and KM-estimated median time to resolution of 27.80 months (95% CI: 22.60, 34.84).

Post-Marketing Data Sources for Bilprevda: up to the DLP (31Mar2026), 0 ONJ events were collected from post-marketing origin.

(2) Severity: Most events leading to adjudication as ONJ were assessed as moderate to severe. Life-threatening events have been reported. In a postmarketing ONJ case registry study with reference denosumab product, most subjects had a maximum reported ONJ severity (American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria), including baseline and all post-baseline assessments, of stage II (65.4%), with a maximum of stage I in 16.5% and a maximum of stage III in 17.4% of enrolled subjects.

(3) Reversibility: In general, ONJ events are clinically reversible. The majority of ONJ cases resolve with denosumab treatment interruption or discontinuation. Surgical treatment may be required; bone resection is not usually necessary.

(4) Long-term outcomes: In a postmarketing ONJ case registry study with reference denosumab product, most of the 282 subjects included in the primary analysis set had either resolution of ONJ (52.5%), had improvement (15.2%), or were stable (24.5%) per AAOMS ONJ staging method.

(5) Impact on quality of life: Discomfort associated with ONJ lesions and/or with more extensive treatments may impact patient wellbeing via decreased oral intake (e.g., decreased hydration and decreased nutritional intake).

Risk factors and risk groups:

Risk factors associated with ONJ include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis.

Preventability:

A dental examination with appropriate preventive dentistry is recommended prior to treatment with denosumab, especially in patients with risk factors. While on treatment, patients should avoid

invasive dental procedures where possible. Patients who are suspected of having or who develop ONJ while on denosumab should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with denosumab, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves. Good oral hygiene practices should be maintained during treatment with denosumab and dental health should be monitored.

Impact on the risk-benefit balance of the product:

The risk of ONJ events has been considered in the product benefit-risk assessment. In light of the product labelling and a Patient Reminder Card that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Significant public health impact is not expected based on the relative frequency observed in clinical trials and with the observations that most ONJ events appear to be moderate to severe in severity and resolve without requiring extensive surgical treatment.

Details of Important Identified Risk 2: Atypical Femoral Fracture

Potential mechanisms:

Prolonged suppression of bone turnover may be associated with increased risk of atypical femoral fracture (AFF), but the pathogenesis remains unclear and causes of AFF are likely multifactorial. Based on nonclinical studies of bisphosphonates, collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodelling, vascularity, and angiogenesis lend biologic plausibility to a potential association between these effects and AFF.

Evidence source(s) and strength of evidence:

This risk has been reported in clinical trials, the scientific literature and is also reflected in the SmPC of the reference medicinal product. This risk was further supported by the reference denosumab post-marketing reports.

Characterisation of the risk:

(1) Frequency: According to the clinical data of the reference medicinal product, in a comprehensive evaluation of denosumab 120 mg clinical trials, 15 subjects experienced 17 events meeting the American Society for Bone and Mineral Research criteria for AFF. This corresponds to 0.2% (15 of 8342) of all subjects who received at least 1 dose of denosumab (Similar results are observed when consideration is limited to studies utilizing monthly dosing throughout [0.1 %, 6 subjects with AFF in 6101 subjects]). All of these adjudicated events of AFF occurred in subjects who received denosumab 120 mg for at least 4 years corresponding to 0.7% (15 of the 2228) of subjects who were followed for 4 or more years.

In the clinical trial program, AFF has been reported uncommonly in patients treated with denosumab 120 mg and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.

In the clinical trial program with reference denosumab product for giant cell tumor of bone, AFFs have been reported commonly in patients treated with denosumab. In a long-term phase 2 open-label clinical trial reference denosumab product in patients with giant cell tumor of bone, incidence of confirmed AFF was 0.95%; 5 of 526 patients exposed to denosumab. In the

follow-up study, the incidence of confirmed AFF was 3.9%; 2 of 51 of patients exposed to denosumab.

Post-Marketing Data Sources for Bilprevda: up to the DLP (31Mar2026), 0 AFF events were collected from post-marketing origin.

(2) Severity: Atypical femoral fracture is a medically important adverse event that generally requires significant medical interventions such as surgery and ongoing monitoring to mitigate risk for and severity of contralateral fractures.
(3) Reversibility: It is unknown if the pathophysiological mechanism(s) contributing to the development of AFF are reversible after treatment is discontinued.
(4) Long-term outcomes: No data on long-term outcomes are available.
(5) Impact on quality of life: As with other hip fractures, AFF can cause short-term or long-term disability. Some data suggests that healing of AFF may be more prolonged than a typical femoral fracture.

Risk factors and risk groups:

Long-term antiresorptive treatment has been associated with AFF. Corticosteroids have also been reported in the literature to potentially be associated with AFF. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.

Preventability:

No data are currently available on potential measures to prevent AFF. Patients using long-term antiresorptives may experience pain over the femur, which requires radiological examination if atypical fracture is suspected.

Impact on the risk-benefit balance of the product:

The risk of AFF events has been considered in the product benefit-risk assessment. In light of the product labelling that has been proposed to minimise this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Based on the frequency of AFF, the size of the indicated populations, and usage patterns of denosumab in clinical practice, no significant additional public health impact is expected.

Details of Important Potential Risk 1: Cardiovascular Events

Potential mechanisms:

Elevated levels of osteoprotegerin (OPG) have been associated with coronary artery disease in cross-sectional studies, but this association has been contradicted by preclinical and epidemiological studies demonstrating that the lack of OPG or unopposed RANKL is associated with cardiac calcification. Because of these conflicting results and because denosumab inhibits RANKL, a theoretical concern for denosumab to affect progression of atherosclerosis exists.

Evidence source(s) and strength of evidence:

This is a theoretical risk based on the epidemiological association between OPG levels and cardiovascular disease which has not been substantiated in the clinical studies or in the post-marketing experience.

Characterisation of the risk:

(1) Frequency: According to the clinical data of the reference medicinal product, in the pooled pivotal SRE Solid Tumour studies, subject incidence of CV adverse events was 29.7% in both treatment groups; the HR was 0.98 (95% CI: 0.89, 1.08). In a pivotal study with denosumab 120 mg Q4W in subjects with castrate-resistant prostate cancer (CRPC), the subject incidence of CV adverse events was 33.1 % in the denosumab group and 27.0% in the placebo group; the HR was 1.23 (95% CI: 1.02, 1.49). In the SRE multiple myeloma study, the subject incidence of adverse events of cardiac disorders was 11.6% in the denosumab group and 13.5% in the zoledronic acid group; the HR was 0.85 (95% CI: 0.65, 1.12). The subject incidence of adverse events of vascular disorder was 20.9% in the denosumab group and 19.8% in the zoledronic acid group; the HR was 1.07 (95% CI: 0.86, 1.31).

    Post-Marketing Data Sources for Bilprevda: up to the DLP (31Mar2026), 0 cardiovascular events were collected from post-marketing origin.

(2) Severity: The majority of CV events were mild to moderate. Life-threatening and fatal events have been reported.

(3) Reversibility: No data on reversibility are available.

(4) Long-term outcomes: No data on long-term outcomes are available.

(5) Impact on quality of life: Cardiovascular disease varies greatly in severity. For severe disease, patients may be hospitalised for treatment and disability may occur.

Risk factors and risk groups:

The reference product denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing CV conditions and, thus, a higher incidence of CV toxicities than that of the general population.

Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors.

Preventability:

Based on clinical data to date, denosumab has not been associated with an increased incidence or severity of CV adverse effects; therefore, no preventive measures are defined. Patients with potential CV events should be managed according to usual standards of care.

Impact on the risk-benefit balance of the product:

The risk of CV events has been considered in the product benefit-risk assessment, and the overall benefit-risk balance is considered to be positive.

Public health impact:

Significant public health impact on CV disease severity or incidence is not expected based on the information from denosumab clinical studies in the advanced cancer and postmenopausal osteoporosis (PMO)/hormone ablation therapy (HALT) settings.

Details of Important Potential Risk 2: Hypercalcaemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons

Potential mechanisms:

The pathogenesis of hypercalcaemia several months after the last dose in patients other than those with GCTB or growing skeletons may be a consequence of the transient increase in bone turnover activity. Upon cessation of denosumab, the disinhibition of RANKL allows for terminal differentiation and activation of osteoclasts, which were suppressed during treatment. In patients with underlying causes for calcium dyscrasias (e.g., subclinical hyperparathyroidism), denosumab discontinuation, with its transient increase in bone remodelling and accompanying release of bone mineral, could theoretically be associated with transient hypercalcaemia in susceptible individuals if the normal homeostatic mechanism regulating serum calcium are not appropriately maintained.

Evidence source(s) and strength of evidence:

This is a theoretical risk based on the mechanism of action which has not been substantiated in the clinical studies or in the post-marketing experience.

Characterisation of the risk:

(1) Frequency: According to the clinical data of the reference medicinal product, cases of hypercalcaemia in the off-treatment period have been reported in clinical studies, but given the disease state of the subjects, as well as other confounding factors, the occurrence of hypercalcaemia in patients other than those with GCTB or with growing skeletons cannot be attributed to discontinuation of denosumab based on available information. As the mechanism for the identified risk in the susceptible populations is not well understood, a theoretical risk remains in other patient groups.

    Post-Marketing Data Sources for Bilprevda: up to the DLP (31Mar2026), 0 hypercalcaemia several months after the last dose in patient other than those with GCTB or growing skeletons events were collected from post-marketing origin.

(2) Severity: Not applicable.

(3) Reversibility: No data on reversibility are available.

(4) Long-term outcomes: No data on long-term outcomes are available.

(5) Impact on quality of life: Patients may present with severe hypercalcaemia requiring hospitalisation. Patients who experience hypercalcaemia may develop complications such acute renal injury.

Risk factors and risk groups:

Patients other than those with GCTB or growing skeletons following cessation of denosumab.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The risk of hypercalcaemia events following treatment discontinuation in patients other than those with GCTB or growing skeletons has been incorporated in the product benefit-risk assessment, and the overall benefit-risk balance remains positive.

Public health impact:

No significant public health impact is expected as the potential events remain in frequent despite extensive market exposure.

SVII.3.2. Presentation of the missing information

Based on the EMA guide on similar biological medicinal products, the RMP should take into account the risks associated with the use of the reference product. To align with the reference product, this section will contain all the missing information described in the EPAR for the reference product, Xgeva®.

Details of Missing Information 1: Use in Patients With Prior Intravenous Bisphosphonate Treatment

Evidence source:

The incidence of ONJ in patients with prior IV bisphosphonate use was similar to that of patients who only received denosumab in a completed study of the reference product. No notable association was evident between ONJ and prior use of bisphosphonates.

Population in need of further characterisation:

There is information from studies in patients with cancer showing that there is no increased risk of serious complications caused by bone metastases in patients who received denosumab following treatment with bisphosphonates. However, more information is needed.

Details of Missing Information 2: Off-label Use in Patients With Giant Cell Tumour of Bone That is Resectable Where Resection is Unlikely to Result in Severe Morbidity

Evidence source:

No formal studies have been completed to determine denosumab's effect on off-label use in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Population in need of further characterisation:

Information is not available on safety in patients with GCTB that is resectable where resection is unlikely to result in severe morbidity.

Part II: Module SVIII - Summary of the safety concerns

Table 10 Summary of safety concerns

Summary of safety concerns	
Important Identified Risks	• Osteonecrosis of the jaw • Atypical femoral fracture
Important Potential Risks	• Cardiovascular events • Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing information	• Use in patients with prior intravenous bisphosphonate treatment • Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are presented in Table 11.

Specific adverse reaction follow-up questionnaires:

Special adverse event follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

Table 11 Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Osteonecrosis of the jaw	Osteonecrosis of the jaw	To monitor the nature of ONJ in patients treated with Bilprevda in the post-marketing environment.
Post-marketing reports of potential atypical fracture	Atypical femoral fracture	To monitor the nature of AFF in patients treated with Bilprevda in the post-marketing environment.

III.2 Additional pharmacovigilance activities

None.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 12 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risk - Osteonecrosis of the jaw	Routine risk communication: • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • Patient Information Leaflet (PIL) Section 2 • PIL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for oral examination, maintenance of good oral hygiene during treatment, management of patients with unavoidable invasive dental procedure, and temporary interruption of treatment if ONJ occurs are included in Section 4.4 of SmPC. Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Identified Risk - Atypical femoral fracture	Routine risk communication: • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for reporting new or unusual thigh, hip, or groin pain is included Section 4.4 of SmPC. Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Potential Risk - Cardiovascular events	Routine risk communication: • Not applicable Other risk minimisation measures beyond the Product Information: • Prescription only.

Safety concern	Routine risk minimisation activities
Important Potential Risk - Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk communication: • Not applicable Other risk minimisation measures beyond the Product Information: • Prescription only.
Missing Information - Use in patients with prior intravenous treatment with bisphosphonate treatment	Routine risk communication: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 Other risk minimisation measures beyond the Product Information: • Prescription only.
Missing Information - Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity	Routine risk communication: • Not applicable Other risk minimisation measures beyond the Product Information: • Prescription only.

V.2. Additional Risk Minimisation Measures

Table 13 Additional Risk Minimisation Measure: Patient Reminder Card

Objectives	Patient Reminder Card will be distributed to address the following risk: • Osteonecrosis of the jaw
Rationale for the additional risk minimisation activity	The purpose of the Patient Reminder Card is to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Bilprevda) injections for cancer-related conditions, including: • To tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment; • To maintain good oral hygiene and receive routine dental check-ups during treatment; • To inform their doctor and tell their dentist that they are being treated with denosumab if they are under dental treatment or will undergo dental surgery; and • To contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge.
Target audience and planned distribution path	Target audience will be the patients prescribed Bilprevda. Patient Reminder Cards will be distributed to prescribers and patients will receive the Card through the prescribers.

Plans to evaluate the effectiveness of the interventions and criteria for success	Monitor and evaluate post-marketing and clinical study safety data and report in periodic safety update reports (PSURs). The distribution of the Patient Reminder Card will be tracked to ensure that it is completed to the distribution plan agreed with national agencies. Additional requests for Patient Reminder Card will also be recorded as an indicator of ongoing use of the Patient Reminder Card. A standard query will be added to the routine follow-up of spontaneously received adverse drug reactions, inquiring about the reporter's awareness of the Patient Reminder Card. By obtaining this information, depending on obtained feedback, a comparison of spontaneous reporting rates and event patterns (event type, severity) between Patient Reminder Card-aware vs unaware reporting sources might be possible.
Evaluation of the effectiveness of risk minimisation activities	No change in risk benefit profile.
Removal of additional risk minimisation activities (if applicable)	Not applicable.

V.3 Summary of risk minimisation measures

Table 14 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk - Osteonecrosis of the jaw	Routine risk minimisation measures: • SmPC Section 4.3 • SmPC Section 4.4, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and temporary interruption are discussed. • SmPC Section 4.8 • SmPC Section 5.1 • PIL Section 2, where recommendations for oral examination, maintenance of good oral hygiene, management of patients with unavoidable invasive dental procedure, and sign of ONJ are discussed. • PIL Section 4, where symptoms of ONJ is discussed. • Prescription only. Additional risk minimisation measures: • Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Important Identified Risk -	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Atypical femoral fracture	• SmPC Section 4.4, where recommendations for reporting new or unusual thigh, hip, or groin pain are discussed. • SmPC Section 4.8 • PIL Section 2, where recommendations for reporting new or unusual thigh, hip, or groin pain is discussed. • PIL Section 4, where signs of thigh bone fracture are discussed. • Prescription only. Additional risk minimisation measures: • None	reactions reporting and signal detection: • Adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • None
Important Potential Risk - Cardiovascular events	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risk - Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information – Use in patients with prior intravenous treatment with bisphosphonate treatment	Routine risk minimisation measures: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing Information - Off-label use in patients with giant cell tumour of bone that	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
is resectable where resection is unlikely to result in severe morbidity	• None	reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Part VI: Summary of the risk management plan

A summary of the RMP of Bilprevda is presented below.

Summary of risk management plan for Bilprevda (Denosumab)

This is a summary of the risk management plan (RMP) for Bilprevda. The RMP details important risks of Bilprevda, how these risks can be minimised, and how more information will be obtained about Bilprevda's risks and uncertainties (missing information).

Bilprevda's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Bilprevda should be used.

This summary of the RMP for Bilprevda should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Bilprevda's RMP.

I. The medicine and what it is used for

Bilprevda is authorised for prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression, or surgery to bone) in adults with advanced malignancies involving bone and for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous administration.

Further information about the evaluation of Bilprevda's benefits can be found in Bilprevda's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/bilprevda.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Bilprevda, together with measures to minimise such risks and the proposed studies for learning more about Bilprevda's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Bilprevda, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Bilprevda is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Bilprevda are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bilprevda. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risks	• Osteonecrosis of the Jaw • Atypical femoral fracture
Important Potential Risks	• Cardiovascular events • Hypercalcaemia several months after the last dose in patients other than those with giant cell tumour of bone or growing skeletons
Missing Information	• Use in patients with prior intravenous bisphosphonate treatment • Off-label use in patients with giant cell tumour of bone that is resectable where resection is unlikely to result in severe morbidity

II.B Summary of important risks

Important Identified Risk: Osteonecrosis of the Jaw	
Evidence for linking the risk to the medicine	This risk has been reported in clinical trials, the scientific literature and is also reflected in the SmPC of the reference medicinal product. This risk was further supported by denosumab post-marketing reports.
Risk factors and risk groups	Risk factors associated with osteonecrosis of the jaw (ONJ) include the use of antiresorptives (particularly aminobisphosphonates delivered by intravenous [IV] dosing), older age, poor dental hygiene, periodontal disease, invasive dental procedures, trauma from poorly fitting dentures, malignancy, chemotherapy (including antiangiogenesis agents such as bevacizumab), radiation to head and neck, corticosteroids, hypercoagulable state secondary to underlying malignancy, smoking and vascular insufficiency due to thrombosis.
Risk minimisation measures	Routine risk minimisation measures

	• SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • Patient Information Leaflet (PIL) Section 2 • PIL Section 4 • Prescription only. Additional risk minimisation measures • Patient Reminder Card

Important Identified Risk: Atypical Femoral Fracture	
Evidence for linking the risk to the medicine	This risk has been reported in clinical trials, the scientific literature and is also reflected in the SmPC of the reference medicinal product. This risk was further supported by denosumab post-marketing reports.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture (AFF). Corticosteroids have also been reported in the literature to potentially be associated with AFF. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis [RA], hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4 • SmPC Section 4.8 • PIL Section 2 • PIL Section 4 • Prescription only. Additional risk minimisation measures • None

Important Potential Risk: Cardiovascular Events	
Evidence for linking the risk to the medicine	This is a theoretical risk based on the epidemiological between osteoprotegerin (OPG) levels and cardiovascular disease association which has not been substantiated in the clinical studies or in the post-marketing experience.
Risk factors and risk groups	The reference product denosumab development program comprises studies of older subject populations (e.g., osteoporosis, cancer) that are likely to have a higher incidence of pre-existing cardiovascular conditions and, thus, a higher incidence of cardiovascular toxicities than that of the general population.

	Risk factors for atherosclerosis include age, gender, ethnicity, family history, elevated lipid levels, cigarette smoking, hypertension, diabetes, and concomitant medications, including antipsychotic agents and cyclooxygenase-2 (COX-2) inhibitors.
Risk minimisation measures	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None

Important Potential Risk: Hypercalcaemia Several Months After the Last Dose in Patients Other Than Those With Giant Cell Tumour of Bone or Growing Skeletons	
Evidence for linking the risk to the medicine	This is a theoretical risk based on the mechanism of action which has not been substantiated in the clinical studies or in the post-marketing experience.
Risk factors and risk groups	Patients other than those with GCTB or growing skeletons following cessation of denosumab.
Risk minimisation measures	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None

Missing Information: Use in Patients With Prior Intravenous Bisphosphonate Treatment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.5 • SmPC Section 5.1 • PIL Section 2 • Prescription only. Additional risk minimisation measures: • None

Missing Information: Off-label Use In Patients With Giant Cell Tumour of Bone That is Resectable Where Resection is Unlikely to Result in Severe Morbidity	
Risk minimisation measures	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Bilprevda.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Bilprevda.

Part VII: Annexes

Table of contents

Annex 4 - Specific adverse drug reaction follow-up forms

Table of Contents

Follow-up Form Title	Version Number	Date of Follow-up Forms Version
Osteonecrosis of the jaw	2.0	May-2026
Post-marketing reports of potential atypical fracture	2.0	May-2026

Note: The follow-up forms in Annex 4 are separately paginated and are not included in the main document's total page count.

DENOSUMAB Core Questionnaire
Osteonecrosis of the Jaw

AER#

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PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

Date of Event Onset

Date of This Report

Gender: ☐Male ☐Female Weight:_____ lb _____ kg

Age at time of event: _____

Event Reported Term

Study No.

☐ Clinical Trial
☐ Post-marketing

DENOSUMAB ADMINISTRATION/ INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication

☐ Postmenopausal osteoporosis
☐ Bone loss from hormone ablation therapy
Please specify diagnosis_____
☐ Advanced cancer with bone metastasis
Please specify cancer_____
☐ Other
Please specify_____
_____
☐ Don't know

Denosumab Dose

☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other Please specify_____
☐ Don't know _____

Denosumab Exposure

Denosumab first administered (date)_____
Last denosumab dose before event (date) _____
☐ Doses of denosumab were skipped ☐ No ☐Yes ☐ Unknown
If yes, please specify_____
☐ Doses of denosumab given after event began ☐ No ☐Yes ☐ Unknown
If yes, date of first dose following start of event _____

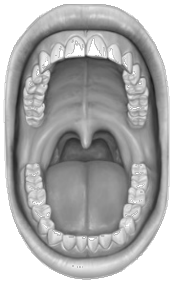
EVIDENCE OF EXPOSED BONE (Please indicate dates as DD/MM/YYYY)

Visible evidence of exposed bone, or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region**:**
☐ No ☐Yes ☐ Unknown; Please describe_____
_____
Date exposed bone was first visualized/probed:_____
Exposed bone or probed bone that has persisted for more than eight weeks:
☐ No ☐Yes ☐ Unknown_____
Prior history of radiation therapy to jaw:
☐ No ☐Yes ☐ Unknown_____
Prior history of metastatic disease to jaw:
☐ No ☐Yes ☐ Unknown
Describe:_____

Please indicate the location of involved area(s) on the diagram at right (mark site(s) clearly with 'X').

Patient's Right **Patient's Left**

Maxilla



Mandible

Please describe location (s):
☐Right maxilla, teeth and lateral jaw
☐Left maxilla, teeth and lateral jaw
☐Right maxilla, medial jaw
☐Left maxilla, medial jaw
☐Right mandible teeth and lateral jaw
☐Left mandible teeth and lateral jaw
☐Right mandible, medial jaw
☐Left mandible, medial jaw
☐Maxilla hard palate
☐Other (specify) _____

Oral Findings

Evidence of infection: ☐ No ☐Yes ☐ Unknown
Please describe_____
Exposed bone at the site of extraction: ☐ No ☐Yes ☐ Unknown
Complete coverage of involved area**(s)** by mucosa: ☐ No ☐Yes ☐ Unknown
If yes, date of complete mucosal coverage_____

CLINICAL SYMPTOMS (Please indicate dates as DD/MM/YYYY)

Date of first clinical signs/symptoms in the mouth (e.g. infection, pain, inflammation): _____
Please describe the clinical signs/symptoms/location:
_____
_____
_____
_____

REPORTER

Name:
Address:
City: State/
Country: Province:
Email: Postal Code:
Phone: (include country code)
Signature:_____
Title_____**Date**_____

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DENOSUMAB Core Questionnaire
Osteonecrosis of the Jaw (continued)

AER#

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PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier

Patient Initials

CONSULTATIONS (Please indicate all dates as DD/MM/YYYY)

Dental / oral surgery / stomatology consultations ☐ No ☐Yes ☐ Unknown If yes, please give date of examination_____

Please provide any consult reports, radiographs, pictures if available _____

TREATMENT INFORMATION (Please indicate what treatments were administered and indicate dates as DD/MM/YYYY)

Antibiotics ☐ No ☐Yes ☐ Unknown If yes, agent(s)/route/dose_____Start date_____Stop date_____

Please describe outcomes of treatment_____

Oral rinses ☐ No ☐Yes ☐ Unknown If yes, agent(s)/dose _____

Please describe outcomes of treatment_____

Oral surgery ☐ No ☐Yes ☐ Unknown If yes, type of surgery_____

Start date_____Stop date_____

Please describe outcomes of treatment_____

Hospitalization ☐ No ☐Yes ☐ Unknown If yes, reason for hospitalization _____

Hospitalization begin date_____Hospitalization end date_____

Please describe outcomes of treatment_____

DENTAL HISTORY (Please indicate all dates as DD/MM/YYYY)

History of poor oral hygiene ☐ No ☐Yes ☐ Unknown _____

Dental extraction recently ☐ No ☐Yes ☐ Unknown If yes, date of procedure_____

Dental surgery recently ☐ No ☐Yes ☐ Unknown If yes, date of procedure_____

Periodontal disease including gingival bleeding, calculus, etc. ☐ No ☐Yes ☐ Unknown Start date_____Stop date_____

Draining fistula in affected area ☐ No ☐Yes ☐ Unknown Start date_____Stop date_____

Dental abscess in affected area ☐ No ☐Yes ☐ Unknown Start date_____Stop date_____

Osteomyelitis in affected area ☐ No ☐Yes ☐ Unknown Start date_____Stop date_____

Root-canal treatment near affected area ☐ No ☐Yes ☐ Unknown If yes, date of treatment_____

Dental treatment, surgery or tooth extraction to the involved area within the last 4-6 months PRIOR to the onset of the oral lesion ☐ No ☐Yes ☐ Unknown

History of dentures/ dental appliance /implant ☐ No ☐Yes ☐ Unknown If yes, please specify ☐ Upper ☐ Lower

Area of lesion at or near a contact point ☐ No ☐Yes ☐ Unknown

MEDICATIONS (Please indicate all dates as DD/MM/YYYY)

PO bisphosphonate ☐ No ☐Yes ☐ Unknown

If yes, agent(s)/dose_____

Start date_____Stop date_____

IV bisphosphonate ☐ No ☐Yes ☐ Unknown If yes, agent(s)/dose _____

Start date_____Stop date_____

Glucocorticoid use within the past 12 months ☐ No ☐Yes ☐ Unknown If yes, agent(s)/dose_____

Start date _____Stop date_____

Immunosuppressant use within the past 12 months ☐ No ☐Yes ☐ Unknown If yes, agent(s)/dose_____

Start date_____Stop date_____

Chemotherapy within the past 12 months☐ No ☐Yes ☐ Unknown If yes, agent(s)/dose_____

Start date_____Stop date_____

Anti-angiogenic agents (e.g. bevacizumab) within the past 12 months ☐ No ☐Yes ☐ Unknown If yes, agent(s)/dose_____

Start date_____Stop date_____

OTHER HISTORY (Please indicate all dates as DD/MM/YYYY)

Current smoker ☐ No ☐Yes ☐ Unknown

If yes, estimated number of pack-years_____

If past smoker, stop date_____

Alcohol consumption ☐ No ☐Yes ☐ Unknown

If yes, estimated of drinks per week_____

Diabetes ☐ No ☐Yes ☐ Unknown If yes, ☐Type I ☐Type II

Patient Reminder Card Status (For EU Patients)

Received a patient reminder card prior to the ONJ event:

☐ Yes ☐ No ☐ Unknown

Version 2.0
Effective Date: 28 May 2026

DENOSUMAB Core Questionnaire
POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE
(low energy, subtrochanteric/femoral shaft fractures)

AER#

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PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate dates as DD/MM/YYYY)

Patient Identifier | Patient Initials | Date of Event Onset | Date of This Report

Gender: ☐Male ☐Female Weight:_____ lb_____ kg

Age at time of event: _____

Study Number (If applicable)

Event

DENOSUMAB ADMINISTRATION / INFORMATION (Please indicate dates as DD/MM/YYYY)

Denosumab Indication:

☐ Postmenopausal osteoporosis

☐ Bone loss from hormone ablation therapy
Please specify diagnosis_____

☐ Advanced cancer with bone metastasis
Please specify cancer_____

☐ Other (Please specify)

☐ Don't know_____

Denosumab Dose ☐ 60 mg SC every 6 months ☐ 120 mg SC every 4 weeks
☐ Other (Please specify)_____ ☐ Don't know

Denosumab Exposure:

Denosumab first administered (date)_____

Last denosumab dose before event (date)_____

Doses of denosumab were skipped ☐Yes ☐ No ☐ Unknown
If yes, please specify_____

Doses of denosumab given after event began ☐Yes ☐ No ☐ Unknown
If yes, date of first dose following start of event_____

DIAGNOSIS (Check all that apply)

Location of fracture:

☐ Femur neck

☐ Femur distal

☐ Femur midshaft

☐ Femur intertrochanter

☐ Femur subtrochanter

☐ Other location (specify): _____

Diagnostic imaging used to confirm fracture:

☐ X-ray ☐ CT scan ☐ MRI

Date of imaging at time of femur fracture (DD/MM/YYYY): _____

☐ Please attach a copy of applicable radiology report(s).

Was this a pathological fracture associated with bone tumor or miscellaneous bone diseases (e.g. Paget's disease, fibrous dysplasia)?

☐ Yes ☐ No ☐ Unknown

Type of fracture:

☐ Transverse

☐ Oblique

☐ Spiral

☐ Not reported

Fracture radiology report includes:

Simple transverse or oblique (30°) fracture with beaking of the cortex:

☐ Yes ☐ No ☐ Not reported

Diffuse cortical thickening of the proximal femoral shaft:

☐ Yes ☐ No ☐ Not reported

Type of trauma reported at time of fracture:

☐ No trauma

☐ Fall from standing height or less

☐ Fall on stairs, steps or curbs

☐ Fall from the height of stool, chair, first rung on a ladder or equivalent (about 20 inches)

☐ Minimal trauma other than a fall

☐ Fall from higher than the height of a stool, chair, first rung on a ladder or equivalent (> 20 inches)

☐ Severe trauma other than a fall (e.g., car accident)

☐ Unknown type of trauma

Early symptom of pain over fracture site:

☐ Pain at site at rest

☐ Pain at site with weight bearing

☐ None

Fracture healed (union) within 6 months ☐ Yes ☐ No ☐ Unknown

If yes:

☐ Date of fracture union (DD/MM/YYYY): _____

☐ Patient able to walk without assistance: ☐ Yes ☐ No ☐ Unknown

☐ Fracture union confirmed through imaging: ☐ Yes ☐ No ☐ Unknown

If yes, check all diagnostic imaging that applies: ☐X-ray ☐CT scan ☐MRI

Version 2.0
Effective Date: 31 Mar 2026

DENOSUMAB Core Questionnaire
POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE
(low energy, subtrochanteric/femoral shaft fractures) (continued)

AER#

PATIENT / CASE ADMINISTRATIVE INFORMATION (Please indicate all dates as DD/MM/YYYY)

Patient Identifier	Patient Initials	Date of This Report

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture:

☐ Non-surgical reduction _____ ☐ Other _____

☐ Casting _____ _____

☐ Surgery _____ ☐ Unknown _____

☐ Revision surgery (2nd surgery) _____ _____

MEDICAL HISTORY/RISK FACTORS (Check all that apply, provide dates and attach relevant reports)

General:

☐ History or current corticosteroid use

☐ Affected hip with prior surgical pinning

☐ Affected hip with prior hip replacement

Cancer:

Evidence of any metastases: ☐Yes ☐No ☐ Unknown

If yes, did metastasis involve bone? ☐ Yes ☐ No ☐ Unknown

Metastasis in femur where fracture occurred? ☐ Yes ☐ No ☐ Unknown

Prior osteoporosis therapy:

☐ Estrogen

☐ Selective estrogen receptor modulator (SERM)

☐ Bisphosphonate (please indicate)

☐ Intravenous ☐ Oral

If yes, how long has therapy been received? (months, years) _____

☐ Parathyroid hormone

Past medical and surgical history: _____

Medication history (include dose, frequency, and dates of treatment): _____

Copies of records/consults/radiology report attached? ☐ Yes ☐ No

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal Code:

Phone: (include country code)

Signature: _____

Title _____ **Date** _____

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Version 2.0
Effective Date: 28 May 2026

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Draft key messages of the additional risk minimisation measures

- **Patient Reminder Card:**

Patient Reminder Cards for osteonecrosis of the jaw (ONJ) will be distributed to prescribers of Bilprevda and patients will receive the Cards through the prescribers.

The Patient Reminder Card is intended to remind patients about important safety information that they need to be aware of before and during treatment with denosumab (Bilprevda) injections for cancer-related conditions, including:

- To tell their doctor/nurse if they have any problems with their mouth or teeth before starting treatment;
- To maintain good oral hygiene and receive routine dental check-ups during treatment;
- To inform their doctor and tell their dentist that they are being treated with denosumab (Bilprevda) if they are under dental treatment or will undergo dental surgery;
- To contact their doctor and dentist immediately if they experience any problems with their mouth or teeth such as loose teeth, pain or swelling, nonhealing of sores, or discharge.

PATIENT REMINDER CARD
Important Safety Information

Patient reminder card regarding osteonecrosis of the jaw (ONJ)

This reminder card contains important safety information that you need to be aware of before and during treatment with denosumab (Bilprevda) injections for cancer-related conditions.

Your doctor has recommended that you receive denosumab (Bilprevda) injections to help prevent bone complications (e.g. fractures) caused by bone metastases, or bone cancers.

A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported commonly (may affect up to 1 in 10 people) in patients receiving denosumab injections for cancer-related conditions. ONJ can also occur after stopping treatment.

It is important to try to prevent ONJ developing as it may be a painful condition that can be difficult to treat. In order to reduce the risk of developing ONJ, there are some precautions you should take:

Before starting treatment:

- Tell your doctor/nurse (health care professional) if you have any problems with your mouth or teeth.
- Check with your doctor whether a dental examination is recommended before you start treatment with Bilprevda.

Patients undergoing chemotherapy and/or radiotherapy, taking steroids or anti-angiogenic medicines (used to treat cancer), undergoing dental surgery, who do not receive routine dental care, have gum disease or who are smokers, may have a higher risk of developing ONJ.

While being treated:

- You should maintain good oral hygiene and receive routine dental check-ups. If you wear dentures you should make sure these fit properly.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Bilprevda.
- Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of ONJ.

Please read the package leaflet that comes with your medicine for further information.

Reporting of side effects

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the package leaflet. You can also report side effects directly via the national reporting system.

By reporting side effects you can help provide more information on the safety of Bilprevda.

Date: May 2026