European Union Risk Management Plan for Bildyos (Denosumab 60 mg)

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission.

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QPPV name: Miroslava Matikova

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.

[redacted]

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Abbreviations

Term/Abbreviation	Explanation
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
CrCL	Creatinine Clearance
CV	Cardiovascular
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GIOP	Glucocorticoid-induced Osteoporosis
GLP-1	Glucagon-Like Peptide-1
HALT	Hormone Ablation Therapy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IgE	Immunoglobulin E
IgG2	Immunoglobulin G2
INN	International Nonproprietary Name
IV	Intravenous
MAH	Marketing Authorization Holder
MOP	Male Osteoporosis
OI	Osteogenesis Imperfecta
ONJ	Osteonecrosis of the Jaw
OPG	Osteoprotegerin
PFS	Pre-filled Syringe
PK	Pharmacokinetic

Term/Abbreviation	Explanation
PL	Package Leaflet
PMO	Postmenopausal Osteoporosis
PSUR	Periodic Safety Update Report
PT	Preferred Term
Q3M	Every 3 Months
Q6M	Every 6 Months
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
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)	Henlius Europe GmbH
Medicinal products to which this Risk Management Plan (RMP) refers	2 Bildyos 60 mg solution for injection in vial; Bildyos 60 mg solution for injection in pre-filled syringe (PFS).
Invented name in the European Economic Area (EEA)	Bildyos (proposed)
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: Bildyos is a fully human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.
	Important information about its composition: Bildyos is a biosimilar to Denosumab (Prolia®).
Hyperlink to the Product Information	Bildyos Product Information (Module 1.3.1)
Indications in the EEA	Current: Not applicable
	Proposed (if applicable): • Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women, Bildyos significantly reduces the risk of vertebral, non-vertebral and hip fractures. • Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Bildyos significantly reduces the risk of vertebral fractures.

	• Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.
Dosage in the EEA	Current: Not applicable
	Proposed (if applicable): The recommended dose of Bildyos is 60 mg administered as a single subcutaneous (SC) injection once every 6 months into the thigh, abdomen or upper arm. Patients must be adequately supplemented with calcium and vitamin D.
Pharmaceutical form(s) and strength(s)	Current (if applicable): Not applicable
	Proposed (if applicable): Bildyos is supplied as a sterile, preservative-free solution intended for SC use (solution for injection). Bildyos is provided in pre-filled syringes or vials at a concentration of 60 mg/mL, filled to a target deliverable volume of 1.0 mL.
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: Prolia®). 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 Prolia® for biosimilarity.

Based on the outcome of the analytical similarity exercise and the in vitro functional/biological assays, the similarity between HLX14 (60 mg, vial) and HLX14 (60 mg, PFS) with Prolia® has been established. As such, the non-clinical data generated for Prolia® 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 Prolia® provide the main data used to support a safety assessment of HLX14. Thus, the data in the summary of product characteristics (SmPC) of Prolia® 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

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

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 • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	**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; 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

Not applicable, to be completed when updating this RMP after authorisation.

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: Prolia®), 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 hypocalcaemia, skin infection leading to hospitalisation, osteonecrosis of the jaw, hypersensitivity reactions, atypical femoral fracture, and hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation.

The important potential risks of HLX14 include fracture healing complications, infection, cardiovascular events, and malignancy.

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

As HLX14 is a biosimilar product, the safety concerns mirror that of the reference medicinal product. No new risks were identified from the clinical trials involving HLX14.

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

Not applicable. As HLX14 is a biosimilar, the safety concerns mirror that of the reference medicinal product denosumab (Trade name: Prolia®). No new risks were identified as a result of the HLX14 clinical trials.

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

Based on the European Medicines Agency (EMA) guide on similar biological medicinal products, the RMP should take into account the risks associated with the use of the reference product. The following risks are the safety concerns of both HLX14 and the reference product, Prolia®.

Important Identified Risk:

- Hypocalcaemia
- Skin infection leading to hospitalisation
- Osteonecrosis of the jaw
- Hypersensitivity reactions
- Atypical femoral fracture
- Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation

Important Potential Risk:

- Fracture healing complications
- Infection
- Cardiovascular events
- Malignancy

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

Not applicable, as this is the initial RMP.

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. So, 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, Prolia®, and from the scientific literature.

Details of Important Identified Risk 1: Hypocalcaemia

Potential mechanisms:

Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.

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, Prolia®:

a) In the pooled pivotal studies for postmenopausal osteoporosis (PMO) and hormone ablation therapy (HALT) subject incidence of hypocalcaemia adverse events was < 0.1% in denosumab-treated subjects and 0.1% in placebo-treated subjects. The incidence of

hypocalcaemia adverse events was lower in denosumab-treated subjects than in placebo-treated subjects; thus, 95% confidence intervals (CIs) were not calculated.

b) In the 24-month final analysis of the glucocorticoid-induced osteoporosis (GIOP) study, subject incidence of hypocalcaemia adverse events was 0.3% in the denosumab group; there were no adverse events of hypocalcaemia in the risedronate group thus, 95% CIs were not calculated.

According to the clinical data of HLX14 studies:

a) In HLX14-001, the incidence of hypocalcaemia adverse events was 10.0% (95%CI: 4.1%-19.5%) in HLX14 group (N=70), the Preferred Term (PT) including Hypocalcaemia and Blood calcium decreased. All subjects experienced Grade 1-2 adverse events. Hypocalcaemia adverse events were considered as related with HLX14 in all subjects. The incidence of hypocalcaemia adverse events was 15.4% (95%CI: 10.5%-21.5%) in Prolia® group (N=182), the PT including Hypocalcaemia and Blood calcium decreased. All subjects experienced Grade 1-2 adverse events. Hypocalcaemia adverse events were considered as related with Prolia® in all subjects.

b) In HLX14-002-PMOP301, the incidence of hypocalcaemia adverse events was 2.7% (95%CI: 1.1%-5.6%) in HLX14 group (N=256), the PT including Hypocalcaemia. All subjects experienced Grade 1-2 adverse events. Hypocalcaemia adverse events were considered as related with HLX14 in 2.3% subjects and as unrelated with HLX14 in 0.4% subjects. The incidence of hypocalcaemia adverse events was 5.0% (95%CI: 2.7%-8.5%) in Prolia® group (N=258), the PT including Hypocalcaemia. All subjects experienced Grade 1-2 adverse events. Hypocalcaemia adverse events were considered as related with Prolia® in 4.3% subjects and as unrelated with Prolia® in 0.8% subjects.

(2) Severity: While most hypocalcaemia events are mild to moderate in severity; severe events have occurred.

(3) Reversibility: Hypocalcaemia is reversible when treated with oral calcium and vitamin D supplementation. In severe cases, intravenous (IV) calcium supplementation may be required.

(4) Long-term outcomes: No long-term complications are anticipated for properly treated hypocalcaemia.

(5) Impact on quality of life: For severe symptomatic hypocalcaemia, patients may be hospitalised for treatment. Generally, patients recover when their hypocalcaemia is treated.

Risk factors and risk groups:

Risk factors include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (CrCL < 30 mL/min), dialysis, and some medications.

Preventability:

Pre-existing hypocalcaemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy, and supplementation with calcium and vitamin D is important during therapy in all patients receiving denosumab. Clinical monitoring of calcium levels is recommended during treatment, especially in those with renal impairment.

Impact on the risk-benefit balance of the product:

The risk of hypocalcaemia has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Significant public health impact is not expected as this risk is preventable and treatable with the appropriate risk mitigating measures communicated clearly in the SmPC.

Details of Important Identified Risk 2: Skin Infection Leading to Hospitalisation

Potential mechanisms:

Keratinocytes can express RANKL and blocking RANKL in mice decreased the number of regulatory T-cells in skin, leading to an increased inflammatory response.

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.

Characterisation of the risk:

(1) Frequency:

According to the clinical data of the reference medicinal product, Prolia®:

a) In pooled PMO/HALT pivotal studies, subject incidence of skin infection was 1.4% with denosumab and 1.3% with placebo; the hazard ratio (HR) was 1.09 (95% CI: 0.78, 1.53). Subject incidence of serious adverse events of skin infection was 0.4% with denosumab and 0.2% with placebo (HR [95% CI] = 2.55 [1.13, 5.76]).

b) In the 24-month final analysis of the GIOP study, subject incidence of adverse events of skin infection was 1.8% with denosumab and 0.5% with risedronate; the HR was 3.62 (95% CI= 0.75, 17.42). Subject incidence of serious adverse events of skin infection was 0.5% in both the denosumab and risedronate groups (HR [95% CI] = 1.03 [0.15, 7.34]).

According to the clinical data of HLX14 studies: No relevant events occurred in HLX14-001 or HLX14-002-PMOP301 studies.

(2) Severity: Serious adverse events of skin infection were mostly severe in intensity.

(3) Reversibility: These events typically resolved with administration of antibiotics.

(4) Long-term outcomes: No long-term complications are anticipated for properly treated patients who are hospitalised due to skin infections.

(5) Impact on quality of life: Requires a hospital stay; patients generally recover with antibiotic treatment.

Risk factors and risk groups:

Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The risk of skin infection leading to hospitalisation has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Since frequency of skin infection leading to hospitalisation is relatively low, absolute difference between denosumab and placebo groups, in reference product's data, is relatively small, and the adverse events can be effectively treated by antibiotics, the negative impact to public health is relatively small.

Details of Important Identified Risk 3: Osteonecrosis of the Jaw

Potential mechanisms:

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.

Characterisation of the risk:

(1) Frequency:

According to the clinical data of the reference medicinal product, Prolia®: No cases of ONJ have been reported in placebo-controlled studies (although cases were reported in open-label extensions to the pivotal PMO study and a HALT study); thus, 95% CIs were not calculated. No cases of ONJ were reported in the GIOP study. Overall, across the clinical development program for the reference medicinal product, positively adjudicated ONJ cases have been reported rarely (18 ONJ cases in 23552 subjects, 0.076%) in subjects cumulatively exposed to denosumab (60 mg) clinical studies.

According to the clinical data of HLX14 studies: No relevant events occurred in HLX14-001 or HLX14-002-PMOP301 studies.

(2) Severity: Most events leading to adjudication as ONJ were assessed as moderate in severity. Mild and severe events were also reported.

(3) Reversibility: In general, ONJ events are clinically reversible with supportive care, antibiotics; however, surgical treatment may be required.

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

(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 include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from

poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, 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.

Impact on the risk-benefit balance of the product:

The risk of osteonecrosis of the jaw has been considered in the product benefit-risk assessment. In light of the product labelling and additional risk minimisation activities addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Significant public health impact is not expected with denosumab, as the event is rare and the actions taken to minimise the likelihood of developing ONJ are described in the prescribing information.

Details of Important Identified Risk 4: Hypersensitivity Reactions

Potential mechanisms:

Two types of allergic reactions, immunoglobulin E (IgE)- and non-IgE-mediated, appear to be related to monoclonal antibody administration. The IgE-mediated reactions can cause both wheal and flare reactions at the injection site, but may also be associated with urticaria and anaphylaxis. The mechanism of non-IgE reactions is unclear.

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, Prolia®:

a) In the pooled PMO/HALT pivotal studies, subject incidence of hypersensitivity and drug hypersensitivity was 1.0% in denosumab-treated subjects and 0.8% in placebo-treated subjects; HR=1.26 (95% CI: 0.83, 1.90). Subject incidence of potential clinical consequences of hypersensitivity was 1.3% in both treatment groups; HR=0.94 (95% CI: 0.66, 1.33).

b) In the 24-month final analysis of the GIOP study, subject incidence of adverse events potentially associated with hypersensitivity was 6.3% in denosumab-treated subjects and 4.7% in risedronate-treated subjects (HR [95% CI] = 1.41 [0.77, 2.59]).

According to the clinical data of HLX14 studies:

a) No relevant events occurred in HLX14-001.

b) In HLX14-002-PMOP301, no relevant events occurred in HLX14 group (N=256). The incidence of hypersensitivity adverse events was 0.4% (95%CI: 0.0%-2.1%) in Prolia® group (N=258), the PT including Dermatitis allergic. The subject experienced Grade 1-2 adverse event and the event was considered as related with Prolia®.

(2) Severity: Most hypersensitivity reactions are mild to moderate in severity; severe events have occurred.

(3) Reversibility: Hypersensitivity reactions are generally reversible with discontinuation of the medication, though treatment may be required.

(4) Long-term outcomes: No long-term complications are anticipated for properly treated hypersensitivity reactions.

(5) Impact on quality of life: For severe hypersensitivity reactions, patients may be treated in the emergency room and/or hospitalised for treatment. Generally, patients recover when denosumab is discontinued with or without additional treatment.

Risk factors and risk groups:

Known hypersensitivity to denosumab and any of its excipients.

Preventability:

No data are available on potential measures to prevent hypersensitivity reactions to denosumab. The appropriate contraindication information on hypersensitivity to denosumab and any of its excipients is included in the SmPC.

Impact on the risk-benefit balance of the product:

The risk of hypersensitivity reactions has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

No significant public health impact is expected as reports of severe events (e.g., anaphylaxis) are rare.

Details of Important Identified Risk 5: 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 the causes of AFF are likely multi-factorial. Based on nonclinical studies, 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.

Characterisation of the risk:

(1) Frequency:

According to the clinical data of the reference medicinal product, Prolia®: No cases of confirmed AFF have been reported in placebo-controlled studies; thus, 95% CIs were not

calculated. In the GIOP study, subject incidence of confirmed AFF was 0.3% (1 event) in the denosumab group; there were no adverse events of AFF in the risedronate group thus, 95% CIs were not calculated. Overall, as of 26Sep2016, adjudicated-positive cases of AFF have been reported rarely (5 of 23280 subjects, 0.021%) in subjects exposed to denosumab (60 mg) in clinical studies.

According to the clinical data of HLX14 studies: No relevant events occurred in HLX14-001 or HLX14-002-PMOP301 studies.

(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. The few events from the reference medicinal product studies leading to adjudication of AFF were considered as severe in intensity.

(3) Reversibility: Atypical femoral fracture is generally treatable with surgical intervention. 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 femur 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 atypical femoral fracture has been considered in the product benefit-risk assessment. In light of the product labelling addressing this risk, the overall benefit-risk balance is considered to be positive.

Public health impact:

Based on the infrequency of AFF in patients treated with denosumab, no significant additional public health impact is expected.

Details of Important Identified Risk 6: Hypercalcaemia in Paediatric Patients Receiving Denosumab and After Treatment Discontinuation

Potential mechanisms:

The exact mechanism of hypercalcaemia occurring in paediatric patients both during the dosing interval and following discontinuation is not certain but may be a consequence of the following, alone, or in combination:

- Hypercalcaemia may result from rapid resorption of retained primary spongiosa in a skeleton with active endochondral ossification. The rate of endochondral ossification and duration of exposure to denosumab would determine the amount of accumulated primary spongiosa that could influence the magnitude of resorptive response (mechanostat-driven) and release of calcium from resorbing bone matrix via an autocrine/paracrine mechanism.
- The magnitude of the resorptive response following treatment and withdrawal in the immature skeleton could be dictated by the normal high rate of bone turnover in individuals with growing skeletons.
- The response of the osteoclast lineage to loss of inhibition of osteoclastogenesis may be intrinsically more robust in individuals with growing skeletons. The increased skeletal metabolism related to bone modelling and growth in children is therefore likely to impact the frequency of hypercalcaemia occurring both between the dosing interval and following discontinuation.

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, Prolia®: In the completed paediatric osteogenesis imperfecta (OI) study during the Q6M dosing regimen, hypercalcaemia was reported for 29 subjects (19.0%). All these events were non-serious. During the Q3M dosing regimen and following denosumab discontinuation, hypercalcaemia was reported for 22 subjects (36.7%). Serious adverse events of hypercalcaemia were reported for 8 subjects (13.3%).

According to the clinical data of HLX14 studies: Not applicable to HLX14-001 or HLX14-002-PMOP301 studies, as only adult subjects were/are studied in both studies.

(2) Severity: Most subjects in the paediatric OI study receiving the Q3M dosing regimen who had hypercalcaemia events experienced mild events. Grade ≥ 3 hypercalcaemia was reported for 10 subjects (16.7%). Grade 4 (Life-threatening) hypercalcaemia was reported for 4 subjects (6.7%).

(3) Reversibility: Hypercalcaemia is reversible when treated. In severe cases, use of rescue medications may be required.

(4) Long-term outcomes: No long-term adverse effects are anticipated for properly treated hypercalcaemia.

(5) Impact on quality of life: Paediatric patients may present with severe hypercalcaemia requiring hospitalisation. Generally, patients recover when the hypercalcaemia is treated.

Risk factors and risk groups:

Paediatric patients with growing skeletons and high bone turnover disease states (such as OI).

Preventability:

Denosumab is not indicated in paediatric patients (age < 18 years) and should not be used in paediatric patients. If used in a clinical trial setting, monitoring for signs and symptoms and periodic serum calcium is advisable.

Impact on the risk-benefit balance of the product:

The benefit-risk profile of Bildyos will be considered same as the reference medicinal product Prolia®, which is not favourable in the paediatric patient population.

Public health impact:

Significant public health impact is not expected as this risk is preventable with the appropriate risk mitigating measures communicated clearly in the SmPC.

Details of Important Potential Risk 1: Fracture Healing Complications

Potential mechanisms:

Because denosumab directly suppresses bone resorption and (indirectly) bone formation, it has the theoretical potential to delay fracture healing.

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, Prolia®:

a) Of the subjects who had nonvertebral fractures in the large pivotal PMO study, fracture healing complications (delayed healing or nonunion) were reported in 2 of 386 subjects in the denosumab group (0.5%) and 5 of 465 subjects (1.1%) in the placebo group.

b) Of the subjects who had nonvertebral fractures in the pivotal study for HALT-breast cancer, fracture healing complications were reported in 0 of 8 subjects in the denosumab group and 1 of 8 subjects (12.5%) in the placebo group. Because of the low incidence of fracture healing complications, 95% CIs were not calculated.

c) No fracture healing complications were reported in male osteoporosis (MOP) study and GIOP study.

According to the clinical data of HLX14 studies: No relevant events occurred in HLX14-001 or HLX14-002-PMOP301 studies.

(2) Severity: This risk has not been substantiated; however, impaired fracture healing could have significant impact on patient wellbeing.

(3) Reversibility: This risk has not been substantiated; however, the effects of denosumab on osteoclasts are fully reversible.

(4) Long-term outcomes: This risk has not been substantiated; however, no long-term impact would be anticipated based on reversibility.

(5) Impact on quality of life: Fracture healing complications can cause short-term or long-term disability. Surgery may be required.

Risk factors and risk groups:

General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of fracture healing complications has been considered in overall assessment supporting a positive benefit-risk profile.

Public health impact:

No significant impact on public health is anticipated.

Details of Important Potential Risk 2: Infection

Potential mechanisms:

RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition. However, no clinically relevant effect of denosumab treatment was observed on peripheral blood immune cell subset profiles in studies in healthy elderly men, postmenopausal women, and postmenopausal women with low BMD. No evidence of a treatment effect of denosumab on immunoglobulin production was observed.

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, Prolia®: In the 24-month final analysis of the GIOP study, subject incidence of infections was 36.3% with denosumab and 36.4% with risedronate; HR=1.06 (0.84, 1.34). Subject incidence of serious adverse events of infection was 5.8% in the denosumab group and 6.5% in the risedronate group (HR [95% CI] = 0.95 [0.54, 1.68]).

According to the clinical data of HLX14 studies:

a) In HLX14-001, the incidence of infection adverse events was 67.1% (95%CI: 54.9%, 77.9%) in HLX14 group (N=70), the PT including Pericoronitis, Periodontitis, Tooth abscess, Gingivitis, Oral herpes, Urinary tract infection, Upper respiratory tract infection and COVID-19. All subjects experienced Grade 1-2 adverse events. Infection adverse events were considered as related with HLX14 in 12.9% subjects and as unrelated with HLX14 in 54.3% subjects. The incidence of infection adverse events was 69.2% (95%CI: 62.0%-75.8%) in Prolia® group (N=182), the PT including Acarodermatitis, Acute sinusitis, Anal infection, Arthritis infective, Bronchitis, Eczema infected, Oral herpes, Paronychia, Periodontitis, Rhinitis, Tinea pedis, Tonsillitis, Urinary tract infection, Gingivitis, Pericoronitis, Gastroenteritis, Upper respiratory tract infection and COVID-19. 68.7% subjects experienced Grade1-2 adverse events and 0.5% subject experienced ≥Grade 3 adverse event. Infection adverse events were considered as related with Prolia® in 4.9% subjects and as unrelated with Prolia® in 64.3% subjects.

b) In HLX14-002-PMOP301, the incidence of infection adverse events was 34.8% (95%CI: 28.9%, 40.9%) in HLX14 group (N=256), the PT including Appendicitis, Complicated appendicitis, Coronavirus infection, Herpes zoster, Hordeolum, Influenza, Nasopharyngitis, Otitis externa, Otitis media, Papilloma viral infection, Periodontitis, Pulpitis dental, Respiratory tract infection, Sinusitis, Tracheitis, Viral hepatitis carrier, Bronchitis, Gastroenteritis, Helicobacter infection, Tonsillitis, Bacteriuria, Vaginal infection, Pharyngitis, Asymptomatic bacteriuria, Pneumonia, COVID-19, Upper respiratory tract infection and Urinary tract infection. 33.2% subjects experienced Grade 1-2 adverse events and 1.6% subjects experienced ≥Grade 3 adverse events. Infection adverse events were considered as related with HLX14 in 3.1% subjects and as unrelated with HLX14 in 31.6% subjects. The incidence of infection adverse events was 33.7% (95%CI: 28.0%-39.8%) in Prolia® group (N=258), the PT including Appendicitis, Bacteriuria, Conjunctivitis, Erysipelas, Folliculitis, Helicobacter infection, Lower respiratory tract infection, Sepsis, Septic shock, Sinusitis, Coronavirus infection, Gingivitis, Herpes zoster, Nasopharyngitis, Periodontitis, Pharyngitis, Pneumonia viral, Pulpitis dental, Rhinitis, Asymptomatic bacteriuria, Pneumonia, Bronchitis, Respiratory tract infection, COVID-19, Upper respiratory tract infection and Urinary tract infection. 32.9% subjects experienced Grade 1-2 adverse events and 0.8% subjects experienced ≥Grade 3 adverse events. Infection adverse events were considered as related with Prolia® in 5.0% subjects and as unrelated with Prolia® in 28.7% subjects.

(2) Severity: The majority of reported events of infection were non-serious. Serious adverse events were most commonly reported as severe in intensity.

(3) Reversibility: Infections when treated appropriately are generally reversible.

(4) Long-term outcomes: Infection generally responds to appropriate treatment and as such no long-term effects are anticipated.

(5) Impact on quality of life: For severe infection, patients may be hospitalised for treatment. Generally, patients recover when their infection is treated.

Risk factors and risk groups:

Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of infection has been considered in the overall assessment which supports a positive benefit-risk profile in the indicated populations.

Public health impact:

No significant public health impact is expected for this unsubstantiated risk as effective treatments are available.

Details of Important Potential Risk 3: 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 data 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, Prolia®: The incidence of cardiovascular (CV) event was comparable between the treatment groups in the pooled analysis.

According to the clinical data of HLX14 studies:

a) No relevant events occurred in HLX14-001 study.

b) In HLX14-002-PMOP301, the incidence of CV adverse events was 3.5% (95%CI: 1.6%, 6.6%) in HLX14 group (N=256), the PT including Angina pectoris, Arteriosclerosis coronary artery, Coronary artery disease and Myocardial ischaemia. 3.1% subjects experienced Grade1-2 adverse events and 0.4% subjects experienced ≥Grade 3 adverse events. CV adverse events were considered as related with HLX14 in 1.2% subjects and as unrelated with HLX14 in 2.3% subjects. The incidence of CV adverse events was 3.5% (95%CI: 1.6%-6.5%) in Prolia® group (N=258), the PT including Arteriosclerosis coronary artery, Coronary artery disease, Angina pectoris and Myocardial ischaemia. 2.7% subjects experienced Grade1-2 adverse events and 0.8% subjects experienced ≥Grade 3 adverse events. CV adverse events were considered as related with Prolia® in 0.4% subjects and as unrelated with Prolia® in 3.1% subjects.

(2) Severity: This risk has not been substantiated; however, cardiovascular events may be severe/life-threatening.

(3) Reversibility: This risk has not been substantiated; however, effects of denosumab to block RANKL are fully reversible.

(4) Long-term outcomes: This risk has not been substantiated; however, cardiovascular events could impact patient long-term outcome.

(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 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:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of cardiovascular events has been considered in overall assessment supporting a positive benefit-risk profile.

Public health impact:

Significant public health impact of Bildyos on cardiovascular disease severity or incidence is not anticipated.

Details of Important Potential Risk 4: Malignancy

Potential mechanisms:

RANK ligand is expressed on activated T and B cells and in the lymph nodes and some reports have described immune modulatory effects of RANKL inhibition; however, in vitro studies of RANK and RANKL activity on a wide range of human tumour types provide no evidence for carcinogenic risk associated with RANKL inhibition. In in vivo rodent cancer models, RANKL inhibition has been shown to have a beneficial effect. If denosumab did affect immune function, a hypothetical association with malignancies linked to immune modulation could exist and would be expected to show the pattern of malignancy associated with immune deficiency.

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, Prolia®:

a) In the pivotal PMO study, the subject incidence of new primary malignancy was 4.8% with denosumab and 4.3% with placebo (HR [95% CI] = 1.11 [0.90, 1.37]).

b) In the pivotal HALT prostate cancer study, the subject incidence of new primary malignancy was 5.1% with denosumab and 4.6% with placebo (HR [95% CI] = 1.08 [0.67, 1.72]), and overall survival was 94.1% in each treatment group (HR [95% CI] = 0.99 [0.65, 1.52]).

c) During the placebo-controlled phase of the MOP study, 4 subjects in the denosumab group (3.3%) and no subject in the placebo group reported events of malignancy. The events were prostate cancer in 3 subjects and basal cell carcinoma in 1 subject. Two prostate cancer cases were likely present at baseline based on past medical history.

d) In the 24-month final analysis of the GIOP study, subject incidence of malignancy was 3.0% with denosumab and 1.8% with risedronate (HR [95% CI] = 1.75 [0.69, 4.44]). Subject incidence of serious adverse events of malignancy was 1.8% with denosumab and 1.6% with risedronate.

According to the clinical data of the HLX14 studies:

a) No relevant events occurred in HLX14-001.

b) In HLX14-002-PMOP301, no relevant events occurred in HLX14 group (N=256). The incidence of malignancy adverse events was 0.4% (95%CI: 0.0%-2.1%) in Prolia® group (N=258), the PT including Cervix carcinoma. The subject experienced ≥Grade 3 adverse event and the event was considered as unrelated with Prolia®.

(2) Severity: Malignancy is a clinically important event requiring medical intervention.

(3) Reversibility: Although some malignancies will respond to treatment, long-term survival will depend upon multiple factors and as such onset of malignancy is rarely considered reversible.

(4) Long-term outcomes: New primary malignancy or progression of existing malignancy may be fatal, life-threatening and long-term outcomes will likely be impacted.

(5) Impact on quality of life: Malignancy can be life-threatening and generally requires intervention, e.g., surgery, chemotherapy, and/or radiotherapy.

Risk factors and risk groups:

General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.

Preventability:

No preventive measures are known.

Impact on the risk-benefit balance of the product:

The potential risk of malignancy has been considered in the product benefit-risk assessment which supports a positive benefit-risk profile in the indicated populations.

Public health impact:

Significant public health impact is not anticipated.

SVII.3.2. Presentation of the missing information

There is no missing information for HLX14.

Part II: Module SVIII - Summary of the safety concerns

Table 8 Summary of safety concerns

Summary of safety concerns	
Important Identified Risks	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation
Important Potential Risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing Information	• None

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 9.

Table 9 Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Hypocalcemia	Hypocalcemia	To monitor the nature of hypocalcemia in patients treated with Bildyos in the post-marketing environment.
Infection	Skin infection leading to hospitalisation Infection	To monitor the nature of skin infections leading to hospitalisation and infections of any type reported in patients treated with Bildyos in the post-marketing environment.
Osteonecrosis of the jaw	Osteonecrosis of the jaw	To monitor the nature of ONJ in patients treated with Bildyos in the post-marketing environment.
Post-marketing reports of potential atypical fracture	Atypical femoral fracture	To monitor the nature of AFF reported in patients treated with Bildyos in the post-marketing environment.
Fracture healing	Fracture healing complications	To monitor the nature of fracture healing complications reported in patients treated with Bildyos in the post-marketing environment.
Malignancy	Malignancy	To monitor the nature of malignancy adverse events reported in patients treated with Bildyos in the post-marketing environment.
Hypersensitivity	Hypersensitivity reactions	To monitor the nature of hypersensitivity reported in patients treated with Bildyos 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 10 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risk - Hypocalcaemia	Routine risk communication: • SmPC Section 4.2, 4.3, 4.4 and 4.8 • Package Leaflet (PL) Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for correction of hypocalcaemia prior to initiating treatment with denosumab, adequate calcium and vitamin D intake, and monitoring of calcium levels during treatment with denosumab are included in SmPC Section 4.4. Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Identified Risk - Skin infection leading to hospitalisation	Routine risk communication: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Identified Risk - Osteonecrosis of the jaw	Routine risk communication: • SmPC Section 4.4 and 4.8 • PL Section 2 and 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 procedures, and temporary interruption of treatment if ONJ occurs are included in SmPC Section 4.4. Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Identified Risk - Hypersensitivity reactions	Routine risk communication: • SmPC Section 4.3 and 4.8

Safety concern	Routine risk minimisation activities
	• PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Identified Risk - Atypical femoral fracture	Routine risk communication: • SmPC Section 4.4 and 4.8 • PL Section 2 and 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 in SmPC Section 4.4. Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Identified Risk - Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk communication: • SmPC Section 4.2, 4.4 and 4.8 • PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Potential Risk - Fracture healing complications	Routine risk communication: • SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Potential Risk - Infection	Routine risk communication: • SmPC Section 4.8 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the Product Information:

Safety concern	Routine risk minimisation activities
	• Prescription only.
Important Potential Risk - Cardiovascular events	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the Product Information: • Prescription only.
Important Potential Risk - Malignancy	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other risk minimisation measures beyond the Product Information: • Prescription only.

V.2. Additional Risk Minimisation Measures

Table 11 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 (Bildyos) injections for osteoporosis and bone loss, including: • The risk of osteonecrosis of the jaw during treatment with Bildyos; • The need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment; • The need to ensure good oral hygiene during treatment; • The need to inform their dentist of treatment with Bildyos and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.
Target audience and planned distribution path	Target audience will be the patients prescribed Bildyos. Patient Reminder Card was 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 distributed in accordance with the 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 12 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk - Hypocalcaemia	Routine risk minimisation measures: • SmPC Section 4.4, where recommendation regarding correction, adequate intake of calcium and vitamin D, and monitoring of calcium levels is provided. • SmPC Section 4.2, 4.3 and 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypocalcaemia Additional pharmacovigilance activities: • None
Important Identified Risk - Skin infection leading to hospitalisation	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • None
Important Identified Risk - Osteonecrosis of the jaw	Routine risk minimisation measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided. • SmPC Section 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for ONJ Additional pharmacovigilance activities: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Patient reminder card	
Important Identified Risk - Hypersensitivity reactions	Routine risk minimisation measures: • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for hypersensitivity Additional pharmacovigilance activities: • None
Important Identified Risk - Atypical femoral fracture	Routine risk minimisation measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided. • SmPC Section 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for AFF Additional pharmacovigilance activities: • None
Important Identified Risk - Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	Routine risk minimisation measures: • SmPC Section 4.2, 4.4 and 4.8 • PL Section 2 • 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 - Fracture healing complications	Routine risk minimisation measures: • SmPC Section 5.3 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for fracture healing complications Additional pharmacovigilance activities: • None
Important Potential Risk - Infection	Routine risk minimisation measures: • SmPC Section 4.8 • PL Section 4 • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for infection Additional pharmacovigilance activities: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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 - Malignancy	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for malignancy Additional pharmacovigilance activities: • None

Part VI: Summary of the risk management plan

A summary of the RMP of Bildyos is presented below.

Summary of risk management plan for Bildyos (Denosumab)

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

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

This summary of the RMP for Bildyos 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 Bildyos ’s RMP.

I. The medicine and what it is used for

Bildyos is authorised for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures, and treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see SmPC for the full indication). It contains denosumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Bildyos’s benefits can be found in Bildyos’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage <link to the EPAR summary landing page>.

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

Important risks of Bildyos, together with measures to minimise such risks and the proposed studies for learning more about Bildyos’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 Bildyos, 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 Bildyos is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Bildyos 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 Bildyos. 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	• Hypocalcaemia • Skin infection leading to hospitalisation • Osteonecrosis of the jaw • Hypersensitivity reactions • Atypical femoral fracture • Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation
Important Potential Risks	• Fracture healing complications • Infection • Cardiovascular events • Malignancy
Missing Information	• None

II.B Summary of important risks

Important Identified Risk: Hypocalcaemia	
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 include severe renal impairment and hyperphosphatemia. Other risks factors may include a history of hypoparathyroidism, parathyroid hormone resistance, vitamin D deficiency or resistance, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment (creatinine clearance < 30 mL/min), dialysis, and some medications.
Risk minimisation measures	Routine risk minimisation measures:

	• SmPC Section 4.4, where recommendation regarding correction, adequate intake of calcium and vitamin D, and monitoring of calcium levels is provided. • SmPC Section 4.2, 4.3 and 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • None

Important Identified Risk: Skin infection leading to hospitalisation	
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.
Risk factors and risk groups	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition. Risk factors for skin infection in older patients include skin wounds, peripheral vascular disease, eczema/dermatitis, and venous stasis disorders.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • None

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.
Risk factors and risk groups	Risk factors include duration of exposure to denosumab, prior bisphosphonate use (particularly for extended periods of time), older age, periodontal disease, dentoalveolar surgery, trauma from poorly fitting dentures, malignancy, chemotherapy, corticosteroids, smoking, systemic or regional infection, immune-compromised state predisposing to increased risk of infection, hypercoagulable state secondary to underlying malignancy, and vascular insufficiency due to thrombosis.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where oral hygiene and dental management guidance is provided. • SmPC Section 4.8

	• PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • Patient Reminder Card

Important Identified Risk: Hypersensitivity reactions	
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	Known hypersensitivity to denosumab and any of its excipients.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3 and 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • None

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.
Risk factors and risk groups	Long-term antiresorptive treatment has been associated with atypical femoral fracture. Corticosteroids have also been reported in the literature to potentially be associated with atypical femoral fracture. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of bisphosphonates, glucocorticoids, and proton pump inhibitors.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4, where recommendation for reporting potential symptoms is provided. • SmPC Section 4.8 • PL Section 2 and 4 • Prescription only. Additional risk minimisation measures: • None

Important Identified Risk: Hypercalcaemia in paediatric patients receiving denosumab and after treatment discontinuation	
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	Paediatric patients with growing skeletons and high bone turnover disease states (such as osteogenesis imperfecta).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2, 4.4 and 4.8 • PL Section 2 • Prescription only. Additional risk minimisation measures: • None

Important Potential Risk: Fracture healing complications	
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	General risk factors for fracture healing complications are thought to include older age, diabetes, use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids, smoking, excessive alcohol use, and poor nutrition.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 5.3 • Prescription only. Additional risk minimisation measures: • None

Important Potential Risk: Infection	
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	Risk factors for infection in general include increasing age, immunosuppression associated with cancer, diabetes, HIV/AIDS, immunosuppressant drugs (e.g., corticosteroids, arthritis medications, and chemotherapy drugs), substance abuse, and malnutrition.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • PL 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 data which has not been substantiated in the clinical studies or in the post-marketing experience.
Risk factors and risk groups	The 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 COX-2 inhibitors.
Risk minimisation measures	Routine risk minimisation measures: • Prescription only. Additional risk minimisation measures: • None

Important Potential Risk: Malignancy	
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	General factors for risk of malignancy include advancing age, diet, cigarette smoking, excessive ethanol consumption, and numerous environmental toxins. In addition, cancer populations are at increased risk for a second primary malignancy because of their existing malignancy, possible genetic predisposition, and exposure to chemotherapy and radiation treatment.
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 Bildyos.

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

There are no studies required for Bildyos.

Annex 4 - Specific adverse drug reaction follow-up forms

Table of Contents

Follow-up Form Title	Version Number	Date of Follow-up Forms Version
Hypocalcaemia	1.0	18-Oct-2024
Infection	1.0	18-Oct-2024
Osteonecrosis of the jaw	1.0	18-Oct-2024
Post-marketing reports of potential atypical fracture	1.0	18-Oct-2024
Fracture healing	1.0	18-Oct-2024
Malignancy	1.0	18-Oct-2024
Hypersensitivity	1.0	18-Oct-2024

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
Hypocalcemia

AER#

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Henlius and Organon do not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number, and government-issued identifier.

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 ☐ 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_____

SIGNS AND SYMPTOMS (Check all that apply)

☐Numbness
(Specify if involving digits and/or peri-oral region)_____

☐ Convulsions ☐ Muscle twitching

☐ Muscle cramping ☐ Paresthesia

☐ Syncope ☐ Tetany

☐ None ☐ Other_____

DIAGNOSIS (Check all that apply)

Serum calcium at time of event:_____mg/dL ☐ Unknown
Please provide serum albumin result _____

Serum albumin at the time of event < 4.0 g/dL?
☐ Yes ☐ No ☐ Unknown
If yes, what were the ionized calcium levels?_____mmol/dL

Serum creatinine at time of event was > 2.0 ×times upper limit of normal?
(Please provide result)_____☐ Yes ☐ No ☐ Unknown
Hypocalcemia-induced EKG changes (QT prolongation)?
☐ Yes ☐ No ☐ Unknown

TREATMENT

Treated only as an outpatient? ☐ Yes ☐ No
If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown
Treated in the ER? ☐ Yes ☐ No
If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown
Treatment included general hospital admission for calcium replacement?
☐ Yes ☐ No ☐ Unknown
If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown
Treatment included ICU admission? ☐ Yes ☐ No ☐ Unknown
If yes, route of calcium replacement: ☐ IV ☐ Oral ☐ Unknown
Overall length of hospital stay:
☐≤1 day ☐> 1 day ☐≤ 7 days ☐>7 days

Anti-arrhythmic medications? ☐ Yes ☐ No ☐ Unknown
If yes, please provide the details such as names and dates of treatment
Anti-arrhythmic medications_____
Other treatment? ☐ Yes ☐ No ☐ Unknown
If yes, specify: _____

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DENOSUMAB Core Questionnaire
Hypocalcemia (continued)

AER#

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

Patient Identifier

Patient Initials

RISK FACTORS (Check all that apply)

Medical History Risk Factors

Does the patient have any of the following risk factors:	☐ YES ☐ NO	If yes, please provide dates and details:
☐ Acute pancreatitis	☐ History of chronic renal disease	
☐ History of parathyroid disease	☐ History of hypoalbuminemia	
☐ History of malignancy (please specify)	☐ Hypoproteinemia	
☐ Hyperphosphatemia	☐ Magnesium deficiency	
☐ Recent surgery	☐ Sepsis	

☐ Vitamin D deficiency (if patient has a history of vitamin D deficiency, were the vitamin D levels normal at the time of event?
Please provide the vitamin D levels at the time of the hypocalcemia event.

☐ Prior hypocalcemia event **(**before denosumab treatment**)**

Please provide dates and details of prior hypocalcemia event

Medication Risk Factors

Antineoplastic agents? (Check which apply): ☐ cisplatin ☐ cytosine arabinoside ☐ Other_____ ☐ None

Antimicrobials? (Check which apply): ☐ pentamidine ☐ ketoconazole ☐ Other _____ ☐ None

Concomitant Medications

Taking vitamin D supplement? ☐ Yes ☐ No ☐ Unknown (Please provide dose and dates)

Taking calcium supplement? ☐ Yes ☐ No ☐ Unknown (Please provide dose and dates)

Other concomitant medications

Hypocalcemia Event Resolved ☐ Yes ☐ No ☐ Unknown

If yes, what date? (DD/MM/YYY)_____

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal Code:

Phone: (include country code)

Signature:_____

Title_____ **Date**_____

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DENOSUMAB Core Questionnaire
Infection

AER#

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 No.

☐ Clinical Trial

☐ Post-marketing

Event Reported Term

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________________

SIGNS AND SYMPTOMS (Check all that apply, provide dates of onset, resolution, if available)

☐ Fever_____________

☐ Cough ____________

☐ Swelling __________

Location___________

☐ Shortness of breath

____

☐ Pain________________

Location____________

☐ Rash_______________

Location____________

☐ Prolonged fatigue_____

☐ Diarrhea____________

☐ Discharge_____

Location______

Description ____

☐ Chills ________

☐ Night sweats___

☐ Other_________

☐ Organ system affected:

☐ Cardiac

☐ Ear/nose

☐ Throat

☐ Gastrointestinal

☐ Respiratory

☐ Musculoskeletal (including joints)

☐ Nervous (cerebrospinal fluid)

☐ Skin Location__________________

☐ Kidney/genito-urinary

☐ Systemic (bacteremia and/or sepsis)

☐ Other_______________________

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please attach copy of report)

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached	
				Y	N

Diagnostic	Results/Units	Reference Range/Units	Date	Report Attached	
				Y	N

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DENOSUMAB Core Questionnaire
Infection (continued)

AER#

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

Patient Identifier

Patient Initials

REPORTS/RELEVANT FINDINGS (Please provide dates, baseline information and indicate attachments if available)

CHECK WHICH INFECTION APPLIES

☐ Cardiac infections
- ☐ Endocarditis_____
- ☐ Pericarditis (purulent; tuberculous)_____
- ☐ Other, please specify:_____

☐ Ear and labyrinth infections
- ☐ Otitis media_____
- ☐ Otitis externa _____
- ☐ Other, please specify:_____

☐ Gastrointestinal/abdominal infections
- ☐ Colitis_____
- ☐ Diverticulitis_____
- ☐ Appendicitis_____
- ☐ Abdominal sepsis (including peritonitis)_____
- ☐ Hepatic abscess_____
- ☐ Hepatitis B _____
- ☐ Hepatitis C _____
- ☐ Other, please specify:_____

☐ Musculoskeletal and connective tissue infections
- ☐ Osteomyelitis_____
- ☐ Septic arthritis_____
- ☐ Other, please specify:_____

☐ Nervous system infections
- ☐ Meningitis_____
- ☐ Encephalitis_____
- ☐ Other, please specify:_____

☐ Respiratory tract infections
- ☐ Pneumonia_____
- ☐ Pulmonary TB_____
- ☐ Lung abscess_____
- ☐ Legionnella pneumonia_____
- ☐ Mycoplasma pneumonia _____
- ☐ Other, please specify:_____

☐ Kidney and genito-urinary tract infections
- ☐Cystitis_____
- ☐ Pyelonephritis_____
- ☐ Urinary tract infection_____
- ☐ Other, please specify:_____

☐ Systemic infections_____
- ☐ Bacteremia_____
- ☐ Sepsis_____
- ☐ Toxic shock syndrome_____
- ☐ Other, please specify:_____

☐ Wound and skin infections
- ☐ Cellulitis _____
- ☐ Erysipelas_____
- ☐ Necrotizing fasciitis_____
- ☐ Abscess_____
- ☐ Other skin infections, please specify:_____

☐ Opportunistic infections
- ☐ Aspergillus (invasive forms only)_____
- ☐ Blastomycosis pulmonary or extra-pulmonary infections_____
- ☐ Candidiasis systemic_____
- ☐ Coccidioidomycosis secondary/systemic_____
- ☐ Cryptococcal infection - pulmonary and non-pulmonary_____
- ☐ Cytomegalovirus - include systemic site_____
- ☐ Herpes simplex (meningitis or encephalitis)_____
- ☐ Herpes zoster (only systemic or disseminated: involving 2 or more dermatomes)_____
- ☐ Histoplasma infections - chronic disseminated or severe acute _____
- ☐ Mucormycosis (=zygomycosis) including infections due to Rhizopus, Mucor and Absidia of lung, genito-urinary tract, kidney, GIT, skin _____
- ☐ Mycobacterium tuberculosis_____
- ☐ Non-tuberculosis mycobacterium_____
- ☐ Nocardia infection - of brain, lungs, kidney, skin_____
- ☐ Paracoccidioides infections of lungs, skin other_____
- ☐ Pneumocystis carinii pneumonia_____
- ☐ Sporotrichosis - disseminated infections_____
- ☐ Toxoplasmosis encephalitis or disseminated_____
- ☐ Other opportunistic infections, please specify:_____

☐ Other infections, please specify:_____

☐ Parasitic evaluation (ova, etc.)_____

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REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal Code:

Phone: (include country code)

Signature:_____

Title_____**Date**_____

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DENOSUMAB Core Questionnaire

Infection (continued)

AER#

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

Patient Identifier

Patient Initials

REPORTS/RELEVANT FINDINGS(Continued) (Please provide dates, baseline information and indicate attachments if available)

DIAGNOSTICS

☐ Cultures done ☐ No ☐ Yes ☐ Unknown
If yes, check which apply:
☐ Blood culture_____
☐ Culture positive ☐ No ☐Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐Viral
☐Pathogen identified: _____

☐ Urine culture
☐ Culture positive ☐ No ☐Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐Viral
☐ Pathogen identified: _____

☐ Sputum culture _____
☐Culture positive ☐ No ☐Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐Viral
☐ Pathogen identified: _____

☐ Synovial culture_____
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐Viral
☐ Pathogen identified: _____

☐ Cerebrospinal fluid culture
☐ Culture positive ☐ No ☐ Yes ☐ Unknown
If yes, which ☐Bacterial ☐Fungal ☐Viral
☐ Pathogen identified: _____
☐ Tissue culture _____
If yes, specify: ☐ Brain ☐ Lung ☐Liver

☐Kidney ☐ Skin ☐ Bone ☐ Other
☐ Culture positive ☐ No ☐Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐ Viral
☐ Pathogen identified: _____

☐ Catheter Tip/Line _____
☐ Culture positive ☐ No ☐Yes ☐ Unknown
If yes, which ☐ Bacterial ☐ Fungal ☐Viral
☐Pathogen identified: _____

☐ PPD placement ☐ No ☐Yes ☐ Unknown
If yes, PPD positive ☐ No ☐Yes☐ Unknown

☐Parasitic evaluation (ova, etc.) ___
☐X-ray ☐ No ☐Yes ☐Unknown __
☐MRI ☐No ☐Yes ☐Unknown ___
☐ CT scan ☐ No ☐Yes ☐ Unknown
_____
☐ Bone scan ☐ No ☐Yes ☐ Unknown
_____
☐ Other _____
☐ Rapid test _____

☐ Serum titres _____

☐Hospital discharge report _____
_____
☐Other consult report _____

_____
☐Provide final diagnosis and treatment, if available (please specify) _____
_____
☐ Outcome and resolution date_____

TREATMENT

☐ ER antibiotics ☐ No ☐ Yes ☐Unknown
If yes, route
☐ IV ☐ Oral ☐SC ☐ Both oral and IV
☐ Required hospital admission
☐ No ☐ Yes ☐ Unknown
☐ ICU admission ☐ No ☐Yes ☐Unknown
If yes, reason for ICU admission_____

Overall length of hospital stay
☐ < 1 day ☐ > 1 day or < 7 days ☐ > 7 days
_____
☐ In-hospital antibiotics
☐ No ☐ Yes ☐ Unknow
☐ If yes, route of administration
☐ IV ☐ Oral ☐ Both oral and IV

☐Other in-hospital treatment
☐ Antivirals ☐ No ☐ Yes ☐ Unknown
If yes, route of administration ☐ IV ☐ oral
☐Antifungals ☐ No ☐ Yes☐ Unknown
If yes, route of administration ☐ IV ☐ oral
☐ Surgery ☐ No ☐ Yes ☐ Unknown
☐Hyperbaric oxygen ☐No ☐Yes ☐Unknown

PATIENT HISTORY/RISK FACTORS （Please provide history, dates, severity of reaction and intervention)

Please specify any post operative complications, chronic disease or infection, etc.
☐ Chronic lung disease _____
☐ Hepatitis _____
☐ Chronic kidney disease_____
☐ Liver disease _____
☐ Congenital infections/malformations _____
☐ Osteomyelitis _____
☐ HIV _____
☐ Diabetes mellitus_____
☐ Cancer (specify)_____
☐ Recent wounds/infections _____
☐ Immunosuppression _____
☐ Known exposure to TNF inhibitors _____
☐ Chemotherapy _____
☐ Malnutrition/failure to thrive _____
☐ Exposure to infectious agents _____
☐ Personal contact ____ ☐ Body fluids_____
☐ Share personal items (razor, needles, etc.) ___
☐ Potentially contaminated food/liquid _____

Exposure to infectious agents (continued)
☐ Hospital acquired_____
☐ Other _____
☐ Steroid exposure _____
☐ Insect/tick bite _____
☐ Drug or IV drug abuse: Type_____
Amount_____
Frequency _____
☐ Alcohol/tobacco use: Type _____
Amount_____
Frequency_____
☐ Indwelling catheters _____
_____
_____
☐ Recent skin injury
_____
_____
☐ Recent travel (specify)
_____
_____

☐ Exposure to animals/zoonotic diseases (exposure to infected animal)_____
☐ Unprotected sex _____
☐ Immobility_____
☐ Indwelling catheters _____
☐ Nursing home resident _____
☐ Occupational exposure _____
☐ Ostomy_____
☐ Post influenza _____
☐ Surgery < 30 days _____
☐ TB exposure _____
☐ Other history/risk factors _____

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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_____

_____

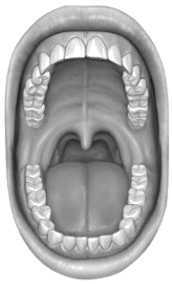
Date exposed bone was first visualized/probed:_____
Exposed bone or probed bone that has persisted for more than eight weeks:
☐ No ☐Yes ☐ Unknown_____
Prior history of radiation therapy to jaw:
☐ No ☐Yes ☐ Unknown_____
Prior history of metastatic disease to jaw:
☐ No ☐Yes ☐ Unknown
Describe:_____

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

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) _____

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

Maxilla



Mandible

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#

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

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DENOSUMAB Core Questionnaire

POSTMARKETING REPORTS OF POTENTIAL ATYPICAL FRACTURE

(low energy, subtrochanteric/femoral shaft fractures)

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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 1.0
Effective Date: 18 Oct 2024

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

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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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DENOSUMAB Core Questionnaire
FRACTURE HEALING

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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)_____ (study #)_____

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, please indicate dates as DD/MM/YYYY)

Date of fracture:_____Date of fracture delayed healing:_____Date of fracture non-healing:

☐ **Fracture to upper body (i.e., above waist)**

Specify location (check all that apply)

☐ Cervical spine
☐ Clavicle
☐ Hand/metacarpal/phalange
☐ Head/face/skull
☐ Humerus
☐ Olecranon
☐ Radius
☐ Rib
☐ Scapula
☐ Shoulder
☐ Sternum
☐ Ulna
☐ Wrist/carpal

☐ Other _____

_____

☐ **Fracture to lower body (i.e., below waist)**

Specify location (check all that apply):

☐ Ankle

☐ Femur (please specify location: neck, subtrochanteric, mid shaft, etc.)

_____

_____

☐ Hip
☐ Patella
☐ Pelvis
☐ Tibia
☐ Fibula

☐ Foot/tarsal/metatarsal/phalange

☐ Other _____

_____

_____

Type of trauma reported at time of fracture (check one):

☐ Severe trauma (e.g., falling from roof, motor vehicle accident)

☐ Minimal trauma (e.g., falling from standing position or less)

☐ Non-traumatic

Characteristics of fracture (check all that apply):

☐ Comminuted
☐ Compound
☐ Pathologic
☐ Poor alignment
☐ Poor immobilization of segments
☐ Soft tissue injury
☐ Unknown

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DENOSUMAB Core Questionnaire
FRACTURE HEALING (continued)

AER#

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

Patient Identifier

Patient Initials

TREATMENT (Please provide dates and indicate attachments if available)

Methods to reduce and set fracture (check all that apply):

☐ Casting _____

☐ Non-surgical reduction _____

☐ Revision surgery (2nd surgery) _____

☐ Surgery _____

☐ Traction _____

☐ Other _____

Did the fracture heal (union)? ☐ Yes ☐ No ☐ Unknown

If yes, provide dale of union (DD/MM/YYYY): _____

If yes, was healing confirmed through imaging? ☐ Yes ☐ No ☐ Unknown

If yes, what diagnostic imaging (check all that apply): ☐ X-rays ☐ CT scan ☐ MRI

If yes, is patient able to walk without assistance? ☐ Yes ☐ No ☐ Unknown

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

☐ Current smoker/tobacco use _____

☐ History or current corticosteroid use _____

☐ Prior fracture history _____

☐ Diabetes _____

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal Code:

Phone: (include country code)

Signature: _____

Title _____ **Date** _____

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AER#

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Office Patient Identifier_____Patient Initials_____

Questionnaire for Malignancy Adverse Events

Date of event onset (DD/MM/YYYY): _____/_____/_____

Is this a new primary malignancy? Yes ☐ No ☐ Unknown ☐

If no, is this a recurrence of a previous cancer? Yes ☐ No ☐ Unknown ☐

Does patient have history of other malignancy? Yes ☐ No ☐ Unknown ☐

If yes, date of prior cancer (DD/MM/YYYY):_____/_____/_____

Tumor stage, if known：_____

Primary site of malignancy:_____

Tumor Stage:

Tumor Size (Check which one applies):

TX ☐ T0☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4 ☐

Tumor Grade (Check which one applies):

GX ☐ G1 ☐ G2 ☐ G3 ☐

Localized (no regional involvement/no distant metastasis)? Yes ☐ No ☐

(If yes, skip next 2 questions)

Lymph Node Involvement (Check which one applies):

NX ☐ N1 ☐ N2 ☐ N3 ☐

Metastases (Check which one applies):

MX ☐ M0 ☐ M1 ☐

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TREATMENT:

Hospitalized?				Yes	☐	No	☐	Unknown ☐
ICU admission?				Yes	☐	No	☐	Unknown ☐
Overall length of hospital stay:	≤ 1 day	☐	> 1 day or ≤ 7	days	☐	> 7 days	☐	
Surgical treatment?				Yes	☐	No	☐	Unknown ☐
Chemotherapy (includes biologics)?				Yes	☐	No	☐	Unknown ☐
Hormonal treatment?				Yes	☐	No	☐	Unknown ☐
Radiation treatment?				Yes	☐	No	☐	Unknown ☐
Bone marrow transplant?				Yes	☐	No	☐	Unknown ☐
If yes, autologous ☐	heterologous	☐						
Was the malignancy treated with curative intention?				Yes	☐	No	☐	Unknown ☐

RISK FACTORS (Check all that apply):

Smoking ☐

Prior Malignancy ☐

Positive Family History (Check all that apply):

Same cancer ☐

Different cancer ☐

Prior therapeutic radiation exposure ☐

Environmental exposure ☐

Specify: _____

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal Code:

Phone: (include country code)

Signature:_____

Title_____ **Date**_____

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DENOSUMAB Core Questionnaire

HYPERSENSITIVITY

AER#

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)_____ (study #)_____

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_____

☐ **Denosumab Antibody Testing Performed:** (provide dates and results)_____

If not performed, do you have interest in antibody testing? ☐ Yes ☐ No_____

SIGNS AND SYMPTOMS (Check all that apply)

☐ Anaphylaxis	☐ Facial edema	☐ Rash	☐ Diarrhea	☐ Tachycardia	☐ Other (specify)
☐ Angioneurotic edema	☐ Hypotension	☐ Shortness of breath	☐ Pruitis	☐ Urticaria	_____
☐ Colic	☐ Laryngeal edema	☐ Stridor	☐ Swelling	☐ Wheezing	_____

EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (please indicate and attach copy of report if available)

Diagnostic	Results/ Units	Reference Range/ Units	Date	Report Attached Y	Report Attached N
Results at BASELINE (prior to Henlius drug)					
CBC with Differential					
WBC					
RBC					
Eosinophils					
Hgb					
Hct					
Platelets					
Other					
Albumin					
Total Protein					
BUN					
Serum Creatinine					
ALT					
AST					
ALP					
Bilirubin					
Calcium					
K^+					
Na^+					
Phosphorus					
Mg++					
Cl·					
CrCl					

Diagnostic	Results/ Units	Reference Range/ Units	Date	Report Attached Y	Report Attached N
Results at TIME OF EVENT					
CBC with Differential					
WBC					
RBC					
Eosinophils					
Hgb					
Hct					
Platelets					
Other					
Albumin					
Total Protein					
BUN					
Serum Creatinine					
ALT					
AST					
ALP					
Bilirubin					
Calcium					
K^+					
Na^+					
Phosphorus					
Mg++					
Cl·					
CrCl					

Version 1.0
Effective Date: 18 Oct 2024

DENOSUMAB Core Questionnaire
HYPERSENSITIVITY (continued)

AER#

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Henlius and Organon do not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number, and government-issued identifier.

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

Patient Identifier

Patient Initials

TREATMENT (Please provide dates and Indicate attachments If available)

☐ER corticosteroids

Route: ☐IV ☐oral

☐ER anti-histaminics

Route: ☐IV only ☐oral only ☐both oral and IV

☐Required hospital admission ☐Yes ☐ No

Overall length of hospital stay

☐< 1 day ☐> 1 day or < 7 days ☐>7 days

☐ICU admission ☐Yes ☐No ☐Unknown

Overall length of hospital stay

☐< 1 day ☐> 1 day or< 7 days ☐> 7 days

☐In-hospital corticosteroids

Route: ☐IV only ☐oral only ☐both oral and IV

☐In-hospital anti-histaminics

Route: ☐IV only ☐oral only ☐both oral and IV

☐Other in-hospital treatment

☐IV vasopressors ☐Yes ☐No ☐Unknown

☐Intubation/mechanical ventilation ☐ Yes ☐No ☐Unknown

☐Hospital admissions/discharge report (please attach if available)

CONCOMITANT MEDICATIONS

☐ACE inhibitors

☐Allopurinol

☐Cancer chemotherapy

☐Dapsone

☐Anticonvulsants (check which apply):

☐Phenytoin

☐Carbamazepine

☐Phenobarbital

☐IV contrast

☐NSAIDS/aspirin

☐Penicillamine

☐Rifampin

☐Antibiotics (check which apply):

☐Beta-lactams including penicillin and cephalosporin

☐Macrolides

☐Sulfonamides

☐ Quinolones

☐ Hypersensitivity event resolved ☐Yes ☐ No ☐Unknown

If yes, date (DD/MM/YYYY):_____

☐ Final diagnosis or etiology (incl. start date). Please send supporting documents for diagnosis_____

☐ Other consult report (please indicate any attachments) _____

REPORTER

Name:

Address:

City: State/

Country: Province:

Email: Postal Code:

Phone: (include country code)

Signature:_____

Title_____ **Date**_____

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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 Card for osteonecrosis of the jaw (ONJ) will be distributed to prescribers of Bildyos and patients will receive the Card 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 (Bildyos) injections for osteoporosis and bone loss, including:

- The risk of osteonecrosis of the jaw during treatment with Bildyos;
- The need to highlight any problems with their mouth or teeth to their doctors/nurses before starting treatment;
- The need to ensure good oral hygiene during treatment;
- The need to inform their dentist of treatment with Bildyos and to contact their doctor or dentist if problems with the mouth or teeth occur during treatment.