LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Xelltempra
# (daptomycin)

# SE/H/2492/01-02/DC

**This module reflects the scientific discussion for the approval of Xelltempra. The procedure was finalised at 2025-09-17. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Xelltempra, 350 mg, 500 mg, powder for solution for injection/infusion.

The active substance is daptomycin. A comprehensive description of the indication and posology is given in the SmPC.

# II. EXECUTIVE SUMMARY

## II.1 About the product

**Mode of action**
Xelltempra is a cyclic lipopeptide natural product that is active against Gram positive bacteria only. The mechanism of action involves binding (in the presence of calcium ions) to bacterial membranes of both growing and stationary phase cells causing depolarisation and leading to a rapid inhibition of protein, DNA, and RNA synthesis. This results in bacterial cell death with negligible cell lysis.

**ATC Classification**
Pharmacotherapeutic group: Antibacterials for systemic use, other antibacterials, ATC code: J01XX09

**Therapeutic indications**
Xelltempra is indicated for the treatment of the following infections (see sections 4.4 and 5.1).
- Adult and paediatric (1 to 17 years of age) patients with complicated skin and soft-tissue infections (cSSTI).
- Adult patients with right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice. See sections 4.4 and 5.1.
- Adult and paediatric (1 to 17 years of age) patients with *Staphylococcus aureus* bacteraemia (SAB). In adults, use in bacteraemia should be associated with RIE or with cSSTI, while in paediatric patients, use in bacteraemia should be associated with cSSTI.

Daptomycin is active against Gram positive bacteria only (see section 5.1). In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Xelltempra should be co-administered with appropriate antibacterial agent(s).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

## II.2 General comments on the submitted dossier

The application for Xelltempra, 350 mg, 500 mg, powder for solution for injection/infusion, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, DK, ES, FR, IS, IT and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Cubicin, 500 mg, powder for solution for injection or infusion, authorised in the Union since 2006, with Merck Sharp & Dohme B.V. as marketing authorisation holder.

## II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

# III. SCIENTIFIC OVERVIEW AND DISCUSSION

## III.1 Quality aspects

**Drug substance**
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

**Drug Product**
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

## III.2 Non-clinical aspects

**Pharmacology/Pharmacokinetics/Toxicology**
Pharmacodynamic, pharmacokinetic and toxicological properties of daptomycin are well known. As daptomycin is a widely used, well-known active substance, no further studies are required. Overview based on literature review is, thus, appropriate.

The applicant provided non-clinical in vitro (a study of primary pharmacodynamics on various bacterial pathogens) and in vivo studies (a single dose pharmacokinetic study in dogs and a 14-day toxicity study in dogs), comparing the product applied for (Xelltempra, 350 mg, 500 mg, powder for solution for injection/infusion) to the reformulated US reference product (Cubicin RF, 500 mg, powder for solution for injection/infusion, "room temperature stable reformulation"). The excipients added for improvement of stability at room temperature differ between Xelltempra (L-histidine, L-arginine and L-isoleucine) and Cubicin RF (sucrose). Preclinical comparisons to a non-EU reference product with other excipients than the EU reference product and the product applied for are not considered relevant and not required. The provided non-clinical data has therefore not been assessed.

**Environmental Risk Assessment (ERA)**
Since Xelltempra is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Xelltempra from a non-clinical point of view.

## III.3 Clinical aspects

**Pharmacokinetics**
To support the marketing authorisation application the applicant has not conducted any bioequivalence studies comparing Xelltempra with the reference product Cubicin.

Pharmacokinetic properties of the active substance
Daptomycin pharmacokinetics are generally linear and time-independent at doses of 4 to 12 mg/kg administered as a single daily dose by 30-minute intravenous infusion for up to 14 days in healthy adult volunteers. Daptomycin administered as a 2-minute intravenous injection also exhibited dose proportional pharmacokinetics in the approved therapeutic dose range of 4 to 6 mg/kg. The terminal half-life is approximately 7-9 hours.

Biowaiver
No bioequivalence study has been submitted. The applicant claims that a bioequivalence study is not necessary according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) since the product is an aqueous parenteral solution.

The product applied for is not qualitatively and quantitatively the same as the reference product with respect to inactive ingredients, as it contains histidine (L-histidine), arginine (L-arginine), and isoleucine (L-isoleucine) which contribute to product stability at room temperature and shorten the reconstitution time of the drug product. In addition, hydrochloric acid is used in minimum quantities for pH adjustment. The applicant states that during the development different in vitro tests showed no complex or micelle formation.

Discussion and overall conclusion
The product applied for is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product. Provided that none of the excipients interact with

the drug substance, no bioequivalence studies are required for this type of product according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1). Complexes can be detected at the concentration of the reconstituted daptomycin solution, but the Applicant has demonstrated using quality data that these complexes are not stable and disappear rapidly upon dilution to plasma concentration which is immediately reached upon injection. Therefore, the biowaiver is considered acceptable.

**Pharmacodynamics/Clinical efficacy/Clinical safety**
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

**Pharmacovigilance system**
Proposed MAH : Xellia Pharmaceuticals ApS

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

**Risk Management Plan**
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Xelltempra.

Part II Safety specification
The MAH has submitted the version 1.1 RMP dated 31 January 2025 and proposed the following summary safety concerns:

**Table 2: Summary of safety concerns**

| | |
|---|---|
| Important identified risks | • None |
| Important potential risks | • None |
| Missing information | • None |

The proposed safety concerns are aligned with those of the reference product Cubicin. This is acceptable.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 1.1 dated 31 January 2025 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

**Periodic Safety Update Report (PSUR)**
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

**Common renewal date**
The common renewal date will be 5 years after closure of the DCP.

# IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Xelltempra, is found adequate. There are no objections to approval of Xelltempra, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

# V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

## V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

**Post approval commitments**
N/A

## V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**
  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**
  N/A

## V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

## V.4 Package Leaflet (PL)

### V.4.1 **Package Leaflet**

The approved PL is available in the MRI Product Index.

### V.4.2 **Assessment of User Testing**

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Daptomycin Xellia 500 mg powder for solution for injection or infusion, UK/H/5250/001-2/DC.

The bridging report submitted by the applicant has been found acceptable.

## V.5 Labelling

The approved Labelling is available in the MRI Product Index.

# VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Procedure number | Scope | Product Information affected (Yes/No) | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| - | - | - | - | - | - |