



## GARDASIL 9 DOSSIER

### *Table of contents of Marketing Authorisation Application dossier (as submitted in EURS)*

#### Module 1

##### 1.0 Cover Letter

1.1 Comprehensive Table of Contents

##### 1.2 Application Form

5. ANNEXED DOCUMENTS (where appropriate)

1. Proof of payment

2. Informed consent medicinal product letter of marketing authorisation holder of authorised medicinal product

3. Proof of establishment of the applicant in the EEA.

4. Letter of authorisation for communication on behalf of the applicant/MAH.

5. (empty)

6. Manufacturing Authorisation required under Article 40 of Directive 2001/83/EC (or equivalent, outside of the EEA where MRA or other Community arrangements apply); any proof of authorisation in accordance with Article 8(k) of Directive 2001/83/EC

7. Copy of the 'Qualification of SME Status

8. Flow-chart indicating all manufacturing and control sites involved in the manufacturing process of the medicinal product and the active substance

9. GMP certificate(s) or other GMP statement(s); Where applicable a summary of other GMP inspections performed

10. Letter(s) of access (LoA) to Active Substance Master File(s) or copy of Ph. Eur. Certificate(s) of Suitability

11. Copy of written confirmation from the manufacturer of the active substance to inform the applicant in case of modification of the manufacturing process or specifications according to Annex I of Directive 2001/83/EC (letter of commitment - LoC).

12. Ph. Eur. Certificate(s) of suitability for TSE



13. Written consent(s) of the competent authorities regarding GMO release in the environment.

**14. Scientific Advice given by CHMP and/or by member state(s)**

15. Copy of Marketing Authorization(s) required under Article 8(j)-(L) of Directive 2001/83/EC in the EEA and the equivalent in third countries on request (a photocopy of the pages which give the marketing authorization number, the date of authorisation and the page which has been signed by the authorizing competent authority will suffice).

16. Correspondence with the European Commission regarding multiple applications

**17. List of Mock-ups or Samples/specimens sent with the application, as appropriate (see Notice to Applicants, volume 2A, chapter 7)**

18. Copy of the Orphan Designation Decision

19. List of proposed (invented) names and marketing authorisation holders in the concerned member states

20. Copy of EMEA certificate for a Vaccine Antigen Master File (VAMF).

21. Copy of EMEA certificate for a Plasma Master File (PMF)

**22. For each active substance, attach a Statement(s) from the Qualified Person of the manufacturing authorisation holder in Section 2.5.1 and from the Qualified Person of each of the manufacturing authorisation holders (i.e. located in EEA) listed in Section 2.5.2 where the active substance is used as a starting material that the active substance is manufactured in compliance with the detailed guidelines on good manufacturing practice for starting materials. Alternatively, such Statement may be signed by one Qualified Person on behalf of all QPs involved (provided this is clearly indicated)**

### 1.3 Product Information

1.3.1 SPC, Labelling and Package Leaflet (publicly available in the SMPc)

**1.3.2 Mock-up**

1.3.3 Specimen

**1.3.4 Consultation with Target Patient Groups**

1.3.5 Product Information already approved in the Member States

1.3.6 Braille

**1.4 Information about the Experts (MOST LIKELY NOT RELEASABLE AS IT CONTAINS THE CVs OF THE EXPERTS WHICH ARE CONSIDERED PPD)**

**1.4.1 Quality**

**1.4.2 Non-Clinical**

**1.4.3 Clinical**

### 1.5 Specific Requirements for Different Types of Applications

- 1.5.1 Information for Bibliographical Applications
- 1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications
- 1.5.3 (Extended) Data / Market Exclusivity
- 1.5.4 Exceptional Circumstances
- 1.5.5 Conditional Marketing Authorisation

#### 1.6 Environmental Risk Assessment

##### 1.6.1 Non-GMO

##### 1.6.2 GMO

#### 1.7 Information relating to Orphan Market Exclusivity

##### 1.7.1 Similarity

##### 1.7.2 Market Exclusivity

#### 1.8 Information relating to Pharmacovigilance

##### 1.8.1 Pharmacovigilance System

##### 1.8.2 Risk-management System

#### 1.9 Information relating to Clinical Trials

#### 1.10 Information relating to Paediatrics

### Responses to Questions

Additional Data

## Module 2 Common Technical Document Summaries

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#### 2.3 Quality Overall Summary - Introduction COMMERCIAL CONFIDENTIAL INFORMATION NON - RELEASABLE

##### 2.3.S Quality Overall Summary - Drug Substance

##### 2.3.S.1 General Information (name, manufacturer)

##### 2.3.S.2 Manufacture (name, manufacturer)

##### 2.3.S.3 Characterisation (name, manufacturer)

##### 2.3.S.4 Control of Drug Substance (name, manufacturer)

##### 2.3.S.5 Reference Standards or Materials (name, manufacturer)

##### 2.3.S.6 Container Closure System (name, manufacturer)

##### 2.3.S.7 Stability (name, manufacturer)

##### 2.3.P Quality Overall Summary - Drug Product

2.3.P.1 Description and Composition of the Drug Product (name, dosage form)

2.3.P.2 Pharmaceutical Development (name, dosage form)

2.3.P.3 Manufacture (name, dosage form)

2.3.P.4 Control of Excipients (name, dosage form)

2.3.P.5 Control of Drug Product (name, dosage form)

2.3.P.6 Reference Standards or Materials (name, dosage form)

2.3.P.7 Container Closure System (name, dosage form)

2.3.P.8 Stability (name, dosage form)

2.3.A Quality Overall Summary - Appendices

2.3.A.1 Facilities and Equipment (name, manufacturer)

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

2.3.A.3 Excipients

2.3.R Quality Overall Summary - Regional Information

2.4 Nonclinical Overview

2.5 Clinical Overview

2.6 Nonclinical Written and Tabulated Summaries

2.6.1 Introduction

2.6.2 Pharmacology Written Summary

2.6.3 Pharmacology Tabulated Summary

2.6.4 Pharmacokinetics Written Summary

2.6.5 Pharmacokinetics Tabulated Summary

2.6.6 Toxicology Written Summary

2.6.7 Toxicology Tabulated Summary

2.7 Clinical Summaries

2.7.1 Summary of Biopharmaceutic and Associated Analytical Methods

2.7.2 Summary of Clinical Pharmacology Studies

2.7.3 Summary of Clinical Efficacy

2.7.4 Summary of Safety

2.7.5 References

2.7.6 Synopses of Individual Studies

## **Module 3 Quality (NON RELEASABLE COMMERCIAL CONFIDENTIAL INFORMATION)**

### **3.1 Module 3 Table of Contents**

### **3.2 Body of Data**

#### **3.2.S DRUG SUBSTANCE**

##### **3.2.S.1 General Information**

###### **3.2.S.1.1 Nomenclature**

###### **3.2.S.1.2 Structure**

###### **3.2.S.1.3 General Properties**

##### **3.2.S.2 Manufacture**

###### **3.2.S.2.1 Manufacturer(s)**

###### **3.2.S.2.2 Description of manufacturing process and process controls**

###### **3.2.S.2.3 Control of materials**

###### **3.2.S.2.4 Controls of critical steps and intermediates**

###### **3.2.S.2.5 Process validation and/or evaluation**

###### **3.2.S.2.6 Manufacturing process development**

##### **3.2.S.3 Characterisation**

###### **3.2.S.3.1 Elucidation of structure and other characteristics**

###### **3.2.S.3.2 Impurities**

##### **3.2.S.4 Control of drug substance**

###### **3.2.S.4.1 Specification**

###### **3.2.S.4.2 Analytical Procedures**

###### **3.2.S.4.3 Validation of analytical procedures**

###### **3.2.S.4.4 Batch analyses**

###### **3.2.S.4.5 Justification of Specification**

##### **3.2.S.5 Reference Standards or Materials**

##### **3.2.S.6 Container Closure System**

##### **3.2.S.7 Stability**

#### **3.2.P DRUG PRODUCT**

##### **3.2.P.1 Description and composition of the drug product**

##### **3.2.P.2 Pharmaceutical Development**

###### **3.2.P.2.4 Controls and critical steps and intermediates**

##### **3.2.P.3 Manufacture**

3.2.P.3.1 Manufacturer(s)

3.2.P.3.2 Batch formula

3.2.P.3.3 Description of Manufacturing Process and Process Controls

3.2.P.3.4 Controls of critical steps and intermediates

3.2.P.3.5 Process validation and / or evaluation

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

3.2.P.4.2 Analytical procedures

3.2.P.4.3 Validation of analytical procedures

3.2.P.4.4 Justification of specifications

3.2.P.4.5 Excipients of human or animal origin

3.2.P.4.6 Novel Excipients (ref to A 3)

3.2.P.5 Control of drug product

3.2.P.5.1 Specification(s)

3.2.P.5.2 Analytical Procedures

3.2.P.5.3 Validation of Analytical Procedures

3.2.P.5.4 Batch analyses

3.2.P.5.5 Characterisation of Impurities

3.2.P.5.6 Justification of specification(s)

3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System

3.2.P.8 Stability

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.3 Excipients

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## Module 4 Nonclinical Study Reports

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#### 4.2.1.2 Secondary Pharmacodynamics

#### 4.2.1.3 Safety Pharmacology

#### 4.2.1.4 Pharmacodynamic Drug Interactions

### 4.2.2 Pharmacokinetics

#### 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)

#### 4.2.2.2 Absorption

#### 4.2.2.3 Distribution

#### 4.2.2.4 Metabolism

#### 4.2.2.5 Excretion

#### 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

#### 4.2.2.7 Other Pharmacokinetic Studies

### 4.2.3 Toxicology

#### 4.2.3.1 Single-Dose Toxicity (in order by species, by route)

#### 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)

#### 4.2.3.3 Genotoxicity

##### 4.2.3.3.1 In vitro

##### 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

#### 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

##### 4.2.3.4.1 Long-term studies (in order by species; including rangefinding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

##### 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeatdose toxicity or pharmacokinetics)

##### 4.2.3.4.3 Other studies

#### 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

##### 4.2.3.5.1 Fertility and early embryonic development

##### 4.2.3.5.2 Embryo-fetal development

##### 4.2.3.5.3 Prenatal and postnatal development, including maternal function

##### 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

#### 4.2.3.6 Local Tolerance

#### 4.2.3.7 Other Toxicity Studies (if available)

- 4.2.3.7.1 Antigenicity
- 4.2.3.7.2 Immunotoxicity
- 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
- 4.2.3.7.4 Dependence
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- 4.2.3.7.7 Other

#### 4.3 Literature References

## Module 5 Clinical Study Reports

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#### 5.2 Tabular Listing of All Clinical Studies

### 5.3 Clinical Study Reports

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- 5.3.1.1 Bioavailability (BA) Study Reports
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#### 5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

- 5.3.2.1 Plasma Protein Binding Study Reports
- 5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies
- 5.3.2.3 Reports of Studies Using Other Human Biomaterials

#### 5.3.3 Reports of Human Pharmacokinetic (PK) Studies

- 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports
- 5.3.3.2 Patient PK and Initial Tolerability Study Reports
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#### 5.3.5 Reports of Efficacy and Safety Studies

##### 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication



5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.3.5.3 Reports of Analyses of Data from More Than One Study

5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case Report Forms and Individual Patient Listings

5.4 Literature References