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保存年限：

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速別：普通件
密等及解密條件或保密期限：
附件：原料藥廠違反GMP警訊乙份(A21020000I105110325400-1.pdf)

主旨：歐洲理事會European Directorate for the Quality of Medicines & HealthCare（EDQM）通報印度原料藥廠「Krebs Biochemicals & Industries Limited」(廠址：Kasimkota Mandal, Visakhapatnam District, India-531 031 Kothapalli, Andhra Pradesh）嚴重違反GMP乙案，詳如說明段，請轉知所屬會員知照。

說明：

一、EDQM併同義大利衛生主管機關Italian Medicines Agency（IMA）查核旨揭原料藥廠，判定嚴重違反GMP，並於105年5月24日正式發布「DECISION TO SUSPEND A CERTIFICATE OF SUITABILITY」，凍結（SUSPEND）「Lovastatin」、「Simvastatin」、「Simvastatin with 0.2% butylated hydroxy anisole」、「Simvastatin held by Jubilant Generics Ltd.」共4個原料藥品項之CERTIFICATE OF SUITABILITY（CEP）品質證明文件。

二、義大利IMA亦於105年4月14日發布「STATEMENT OF NON-COMPLIANCE WITH GMP」，受影響之原料藥品項為「Simvast

atin」。（詳如附件）

三、承上，且義大利IMA已啟動相關後續處置，包括：

(一)評估使用受影響原料藥之製劑產品是否回收，及是否有可替代之原料來源與缺藥疑慮；鑒於該廠違反GMP，已入庫之該廠原料藥，製劑廠應重新執行完整再驗程序。

(二)除非無可替代之供應商及有缺藥之疑慮，旨揭藥廠原料藥應暫停出貨。

(三)旨揭藥廠任何新申請或進行中之申請案將不予核定。

四、鑒於旨揭原料藥廠之製造品質無法符合GMP之要求，可能對藥品製造品質帶來影響與危害，請轉知所屬會員釐清相關輸台製劑產品是否使用旨揭原料藥廠所生產原料藥，並應依說明段三所述辦理。

正本：中華民國西藥商業同業公會全國聯合會、中華民國西藥代理商業同業公會、台北市西藥代理商業同業公會、中華民國開發性製藥研究協會、中華民國藥品行銷暨管理協會

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Italian Medicines Agency

Report No: *IT/NCR/API/2/2016*

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer [1]

Part 1

Issued following an inspection in accordance with :
Art. 111(7) of Directive 2001/83/EC as amended

The competent authority of Italy confirms the following:
The manufacturer: ***KREBS BIOCHEMICALS & INDUSTRIES LTD, Plant Unit II***
Site address: ***Kothapalli Village, Kasimkota Mandal, Visakhapatnam, Andhra Pradesh, 531 031, India***

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2016-03-11*** , it is considered that **it does not comply with the Good Manufacturing Practice** requirements referred to in

- The principles of GMP for active substances referred to in Article 47 of Directive 2001/83/EC .

[1] *The statement of non-compliance referred to in paragraph 111(7) of Directive 2001/83/EC and 80(7) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.*

Part 2

1 NON-COMPLIANT MANUFACTURING OPERATIONS	
Include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;	
1.4	**Other products or manufacturing activity**
	1.4.1 Manufacture of 1.4.1.4 Other: Active substances(en)

Manufacture of active substance. Names of substances subject to non-compliant :
SIMVASTATINA(it) / SIMVASTATIN(en)

3. NON-COMPLIANT MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES	
Active Substance : SIMVASTATIN	
3.1	**Manufacture of Active Substance by Chemical Synthesis**
	3.1.3 Salt formation / Purification steps : Crystallisation
3.5	**General Finishing Steps**
	3.5.1 Physical processing steps : Drying, milling, sieving 3.5.2 Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3.5.3 Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)
3.6	**Quality Control Testing**
	3.6.1 Physical / Chemical testing 3.6.2 Microbiological testing excluding sterility testing

Part 3

1. Nature of non-compliance:
24 deficiencies were identified in total. Five of them were classified as major. The combination of the findings demonstrated a critical risk to public health, as the weaknesses of the company's quality management system and the approach in several GMP areas such as facilities, material management, quality of the water used in the production and QC tests, were not robust enough to sustain a GMP compliant level. The five major deficiencies were identified in the following areas: • One in deviation management; • One in personnel training; • One in facilities; • One in finished product storage management; • One in production and monitoring of purified water.
Action taken/proposed by the NCA **Recall of batches already released** Each involved NCA should evaluate, following assessment conducted in conjunction with MAHs, if a recall of medicinal product is needed. Evaluation should take into account if there are alternative suppliers and potential risk of shortage. Given the nature of non-compliance, assessment should include a complete retest of all imported batches of active substance.

Prohibition of supply
Prohibition of supply is recommended, unless there are not alternative suppliers and there is a risk of shortage.

Suspension or voiding of CEP (action to be taken by EDQM)
Assessment of the findings of the EDQM inspection is currently on going: all CEP's suspension recommended by the inspection team was officially endorsed by the Ad Hoc Committee on 30 March 2016.

Others
This supplier should not be approved in any new/ongoing application.

2016-04-14

Name and signature of the authorised person of the Competent Authority of Italy

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