Modificazione dell'autorizzazione all'immissione in commercio del medicinale «Fraxiparina»

Estratto determinazione V&A/N/V n. 331 del 25 febbraio 2011

Titolare AIC: GLAXOSMITHKLINE S.P.A. con sede legale e domicilio fiscale in Via A. Fleming, 2, 37135 - VERONA (codice fiscale 00212840235)

Medicinale: **FRAXIPARINA**

Variazione AIC: 31.b Aggiunta di nuovi limiti e prove in corso di lavorazione applicati durante la produzione del medicinale
32.c Modifica della dimensione dei lotti del prodotto finito (altri casi)
33. Modifica minore della produzione del prodotto finito
Aggiunta/sostituzione di officina di produzione del prodotto finito per tutte o alcune fasi della produzione

L'autorizzazione all'immissione in commercio è modificata come di seguito indicata:

DA	A
3.2.P.3.1 Manufacturers Manufacture and primary packaging: Glaxo Wellcome Production 1, rue de l'Abbaye 76960 Notre Dame de Bondeville France Cartoning, QC testing and batch release: Glaxo Wellcome Production 1, rue de l'Abbaye 76960 Notre Dame de Bondeville France	**3.2.P.3.1 Manufacturers** **Manufacture, Primary Packaging and Quality Control:** Glaxo Wellcome Production 1, rue de l'Abbaye 76960 Notre Dame de Bondeville France **or** **Catalent Belgium SA** **Font Saint Landry, 10** **1120 Brussels** **Belgium** **Secondary packaging and batch release:** Glaxo Wellcome Production 1, rue de l'Abbaye 76960 Notre Dame de Bondeville France

3.2.P.3.3 Description of Manufacturing Process and Process Controls Stage 0: Preliminary Inspections All starting materials used in the manufacture of the medicinal product must comply with the standards specified. All equipment and facilities are cleaned and/or sterilised in compliance with the in-house standard operating procedures Stage 1: ~~Preparation of the manufacturing tank~~ Wash with purified water or with water for injections and rinse the ~~manufacturing tank~~ with water for injections ~~then decontaminate with steam at 110°C for 100 minutes (or equivalent validated cycle)~~. Stage 2: Dissolution of Nadroparin calcium ~~In the manufacturing tank, equipped with a mixer~~, place approximately 80% of the final volume of Water for Injections ~~warmed to 30 – 40°C.~~ Then add Nadroparin calcium the whole amount, ~~taking care to incorporate the active ingredient slowly, with stirring.~~ Adjust the volume to ~~approximately 95%~~ of the final volume with Water for Injections. ~~Mix the solution slowly and cool to 20-25°C.~~	**3.2.P.3.3 Description of Manufacturing Process and Process Controls** Stage 0: Preliminary Inspections All starting materials used in the manufacture of the medicinal product must comply with the standards specified. All equipment and facilities are cleaned and/or sterilised in compliance with the in-house standard operating procedures. Stage 1: **Preparation of the tanks, filling and filtration equipment** Wash with purified water or with water for injections and rinse the **tanks** with water for injections **then sterilise by steam in compliance with in-house standard operation procedures.** Stage 2: Dissolution of Nadroparin calcium **In the compounding tank,** place approximately 80% of the final volume of Water for Injections **at 20-25ºC.** Then add the whole quantity of Nadroparin calcium. Adjust the volume to **94%** of the final volume of Water for Injections **at 20-25ºC and allow the solution to mix for 30-45 minutes.**

Stage 3: pH Adjustment Prepare a 1% (w/V) solution of calcium hydroxide by adding with slow stirring calcium hydroxyde in a second manufacturing tank containing water for injections. Mix for at least 10 minutes. Allow the solution to stand, carry out the filtration with a 0.2 µm pore size cartridge (a prefiltration with a 0.45 µm pore size filter may be used). Then adjust the pH of the active ingredient solution using the calcium hydroxide solution. The pH obtained should be in the range 7.0 to 7.5. Note: If pH of the solution exceeds, it is possible to readjust it with diluted Hydrochloric Acid. The calcium hydroxide solution may be prepared in advance for one or several batches. It will be stored at +4°C until used in a glass bottle for a maximum of 2 months or any other validated conditions. Stage 4: Completion to volume Adjust to the final volume by adding water for injections. Close the tank. With continuous stirring, increase the temperature to 30-40°C without exceeding 50°C and maintain this temperature for approximately 15 minutes. Stage 5: Prefiltration Carry out prefiltration of the solution by passing through an enclosed nylon filter of 0.2 µm pore size (or equivalent validated filter) under pressure with nitrogen or with peristaltic pump.	Stage 3: pH Adjustment Adjust the pH of the active ingredients solution using the calcium hydroxide solution and allow the solution to mix for 15-25 minutes. The pH obtained should be in the range of 7.2 to 7.4.1 Adjust the volume to 98% of the final Water for Injections at 20-25ºC and allow the solution to mix for 15-25 minutes. Allow the solution to rest for 60-75 minutes. The calcium hydroxide solution may be prepared in advance for one or several batches. It will be stored at +4°C until used in a glass bottle for a maximum of 2 months or any other validated conditions. 1 Note if the pH of the solution is less than 7.2 this step should be repeated. Stage 4: Completion to volume Adjust to the final volume by adding the Water for Injections at 20-30ºC. Nitrogen low oxygen overlapping is applied at the end of the compounding operation. Stage 5: Prefiltration Carry out prefiltration of the solution into two storage tanks by passing through an enclosed nylon filter of 0.2 µm pore size (or equivalent validated filter) under pressure with nitrogen low oxygen or with peristaltic pump.

Stage 6: Sterilising filtration Filter the solution under sterile conditions through a sterile nylon filter of 0.2 µm pore size (or equivalent validated filter). Check the filtration pressure and the integrity of the filter before and after filtration. Collect the filtered solution in a sterile area (Grade A) in a suitable validated sterile container. Maximum holding times for the solution before distribution have been validated by media-fills: ten weeks for the sterile filtered solution collected in sterile glass bottles eight weeks for the sterile filtered solution collected in stainless steel tank Other storage conditions and storage period could be applied if they have been validated by media-fills.	Stage 6: Sterilising filtration Filter the solution through two sterile nylon filters of 0.2 µm pore size (or equivalent validated filter) using a peristaltic pump. Check the filtration pressure and the integrity of the filter before and after filtration. Collect the filtered solution in an aseptic area (Grade A) in a suitable validated sterile container.

Stage 7: Preparation of the immediate packaging components Needle shields: Needle shields are supplied washed, dried and siliconised. Syringe barrels: In an automatic washing machine, wash, rinse in water, dry in hot air (approximately 140°C) and siliconise the inside of the syringe barrels with silicone 1000 cSt and the needles with silicone 12 500 cSt. Then either: Position the needle shields on the syringe barrels. Arrange the syringes in suitable boxes and sterilise in an autoclave at 125°C for 75 minutes (or an equivalent validated cycle). Or: Sterilise the needle shields: moist heat sterilisation at 121°C for 60 minutes (or equivalent validated cycle). Sterilise the syringe barrels: moist heat sterilisation at 125°C for 30 minutes (or equivalent validated cycle). Gather the components under sterile conditions. Plunger stoppers: If necessary, siliconise the plunger stoppers sterilise in an autoclave at 121□C for 60 minutes (or equivalent validated cycle) including a suitable validated drying cycle. The manufacturing process described in this dossier may be simplified by using syringes supplied already equipped with sterile and ready for use needle shields and plunger stoppers. The immediate packaging components processed and tested in this way are introduced directly into this of the process without other preparation. Filling and Stoppering The filling operation is performed under sterile conditions in a validated, Grade A, vertical laminar air flow cabinet or isolator, in accordance with in-house standard operating procedures and European cGMP Annex 1 'Manufacture sterile medicinal product'. Fill the sterile syringes with sterile Nadroparin Calcium 9500 IU AXa/mL solution on an automatic filling machine in accordance with standard operating procedures, so as to guarantee the nominal volume. Stopper immediately, using the sterile plunger stoppers.	Stage 7: Filling and Stoppering The filling operation is performed under sterile conditions in a validated, Grade A, vertical laminar air flow cabinet RABS, in accordance with in-house standard operating procedures and European cGMP Annex 1 'Manufacture sterile medicinal product'. Fill the sterile syringes with Nadroparin Calcium 9500 IU AXa/mL solution on an automatic filling machine in accordance with standard operating procedures, so as to guarantee the nominal volume. Stopper immediately, using the sterile plunger stoppers. Preparation of the primary packaging components The syringes are supplied Sterilized, Clean and ready to Fill. Syringes are equipped with sterile and ready for use needle shields. The plunger stoppers are supplied in Bulk, Sterilized, Clean and ready to Fill. The immediate packaging components processed and tested in this way are introduced directly into the process without other preparation.

Batch Size Glaxo Wellcome Production, Notre Dame de Bondeville, France 160 Litres and 500 Litres	**Batch Size** Glaxo Wellcome Production, Notre Dame de Bondeville, France 160 Litres and 500 Litres **Catalent Belgium SA, Brussels, Belgium** **360 Litres**

3.2.P.3.4 Control of Critical Steps and Intermediates Control of Critical Steps The in-process controls are performed in compliance with Good Manufacturing Practice. The following in-process control parameters are monitored. <u>Stage 0: Preliminary inspections</u> Cleanliness of equipment and premises. ~~Ingredients, production and filling equipment are prepared in a Grade C air quality area which is regularly tested in accordance with in-house standard operating procedures for the production sequence.~~ <u>Stage 1:~~ Preparation of the manufacturing tank~~</u> Check the temperature and duration of decontamination. <u>Stage 2: Dissolution of Nadroparin Calcium</u> Check the temperature of the Water for Injections ~~(≥ 30° C)~~. ~~Check the temperature after cooling (20 – 25° C)~~ Check that dissolution is complete: visual test. <u>Stage 3: pH adjustment</u> Check the duration of the mixing of ~~calcium hydroxide with water for injections.~~ ~~Perform an integrity test of the filter before and after use.~~ Check the pH of the Nadroparin Calcium solution after adjustment: ~~7.0 to 7.5~~, in accordance with Ph. Eur ~~(2.2.3)~~.	**3.2.P.3.4 Control of Critical Steps and Intermediates - Control of Critical Steps** The in-process controls are performed in compliance with Good Manufacturing Practice. The following in-process control parameters are monitored. <u>Stage 0: Preliminary inspections</u> Cleanliness of equipment and premises. <u>Stage 1: **Preparation of the tanks, filling and filtration equipment**</u> Check the temperature and duration of decontamination. <u>Stage 2: Dissolution of Nadroparin Calcium</u> Check the temperature of the Water for Injections **(20 - 25° C)**. Check that dissolution is complete: visual test. <u>Stage 3: pH adjustment</u> Check the duration of the mixing of **calcium hydroxide solution with the active ingredients solution.** Check the pH of the Nadroparin Calcium solution after adjustment: **pH 7.2 to 7.4**, in accordance with Ph. Eur.

Stage 4: Completion to final volume Check the temperature of the aqueous solution (approximately 30-40°C) made up to the final volume and duration of mixing (approximately 15 minutes). Stage 5: Prefiltration Bioburden (bacterial count) is tested prior to filtration (≤ 100 cfu/L) according to Ph. Eur.(2.6.12). Stage 6: Sterilising filtration Perform an integrity test of the filter before and after filtration. Stage 7: Filling and Stoppering Check the conformity of the sterilisation cycles of the immediate packaging articles. Check that the sterile area and the sterility of the equipment used for filling the product conform to the in-house standard operating procedures of the production site, corresponding to Grade A. This procedure is regularly monitored. Filling: The fill volume is periodically checked in order to guarantee a minimum extractable volume of 0.2, 0.3, 0.4, 0.6, 0.8 or 1mL according to fill size.	Stage 4: Completion to final volume Check the temperature of the aqueous solution (approximately 20 - 30°C) made up to the final volume. Stage 5: Prefiltration Perform an integrity test of the filter before and after filtration. Stage 6: Sterilising filtration Perform an integrity test of the filter before and after filtration. Bioburden (bacterial count) is tested prior to filtration (≤ 10 cfu/100mL) according to Ph. Eur. Stage 7: Filling and Stoppering Aseptic area conformance to Grade A and sterility of the equipment used for filling the product are assured by site standard operating procedures. These procedures are regularly monitored. Filling: The fill volume is periodically checked in order to guarantee a minimum extractable volume of 0.2, 0.3, 0.4, 0.6, 0.8 or 1mL according to fill size.

relativamente alle confezioni sottoelencate:
AIC N. 026736064 - "2850 ui antixa/0,3 ml soluzione iniettabile" 6 siringhe preriempite 0,3 ml
AIC N. 026736076 - "3800 ui antixa/0,4 ml soluzione iniettabile" 6 siringhe preriempite 0,4 ml
AIC N. 026736088 - "5700 ui antixa/0,6 ml soluzione iniettabile" 10 siringhe preriempite 0,6 ml

AIC N. 026736090 - "7600 ui antixa/0,8 ml soluzione iniettabile" 10 siringhe preriempite 0,8 ml
AIC N. 026736102 - "9500 ui antixa/1 ml soluzione iniettabile" 10 siringhe preriempite 1 ml

I lotti già prodotti possono essere mantenuti in commercio fino alla data di scadenza indicata in etichetta.

La presente determinazione ha effetto dal giorno successivo a quello della sua pubblicazione nella Gazzetta Ufficiale della Repubblica Italiana.

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