SPECIALITÀ MEDICINALI
PRESIDI SANITARI E MEDICO-CHIRURGICI

BAYER - S.p.a.

Modifiche secondarie di un'autorizzazione all'immissione in commercio di una specialità medicinale per uso umano. (Modifiche apportate ai sensi del decreto legislativo 29 dicembre 2007, n. 274).

Titolare: Bayer Schering Pharma AG, Muellerstrasse 178, Berlino, rappresentante in Italia: Bayer S.p.A.,con sede e domicilio legale in Viale Certosa, 20156 (Milano) Codice Fiscale e Partita I.V.A. n.05849130157

Specialità medicinale: **ULTRAVIST**

Confezione e numero di AIC:

«150 mg/ml soluzione iniettabile» 1 flacone 200 ml - A.I.C. n.026965121;

«240 mg/ml soluzione iniettabile» 1 flacone 50 ml - A.I.C. n.026965018.

Modifiche apportate ai sensi del regolamento CE 1084/03.

1. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: NIP-monoamide moist: Manufacturing procedure: 5. If the substance does not meet the specification requirements, make it into a slurry with water, dissolve it with aqueous sodium hydroxide, 50 % (w/w) at a pH of between 9 and 10, then process further as described in the MFDS.

A: NIP-monoamide moist: Manufacturing procedure: 6. In case of quality relevant deviations in the manufacturing process the batch has to be checked. If the substance does not meet the specification requirements, make it into a slurry with water, dissolve it with aqueous sodium hydroxide, 50 % (w/w) at a pH of between 9 and 10, then process further as described in the MFDS.

2. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: AMIP-monoamide: Manufacturing procedure: Treat the solution of substance with palladium catalyst, 5 %, on charcoal, type 101 N/NW

and, while stirring strongly pass in hydrogen at an internal temperature of max. 97 °C and hydrogenate until no more hydrogen is absorbed.

A: AMIP-monoamide: Manufacturing procedure: Treat the solution of substance with palladium catalyst and, while stirring strongly pass in hydrogen at a temperature of max. 97 °C and hydrogenate until no more hydrogen is absorbed.

3. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

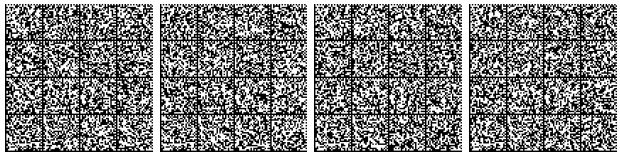
Da: TAMIP-monoamide: Manufacturing procedure: [...] (old manufacturing process description) Alternative reaction: [...] Add the remaining amounts of AMIP monoamide solution and iodine monochloride simultaneously, within 45 to 90 min, inoculate with TAMIP monoamide and stir for 8 to 12 hours at 62 to 68 °C. Further processing as described below. Further processing: While cooling, add sodium bisulfite solution and stir for two hours. [...] Isolate the crystal suspension, wash with water and dry at a temperature not exceeding 70°C.

A: TAMIP-monoamide: Manufacturing procedure: --- (old manufacturing process deleted) [...] Add the remaining amounts of AMIP monoamide solution and iodine monochloride simultaneously, within 45 to 90 min, at 62 to 68 °C, inoculate with TAMIP monoamide, if necessary, and stir. While cooling, add sodium bisulfite solution and stir. [...] Isolate the substance, wash and dry at a temperature not exceeding 70 °C.

4. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: TAMIP-diacetate: Yield: 1280 to 1553 kg

A: TAMIP-diacetate: Yield: 1430 to 1750 kg



5. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo e conseguente Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: Manufacturing procedure: Centrifuges with a layer of kieselgur can also be used. TIP diamide chloride: Manufacturing procedure: TAMIP diacetate, containing kieselgur, can also be used.

A: Manufacturing procedure:--- (deletion of Centrifuges with a layer of kieselgur can also be used). TIP diamide chloride: Manufacturing procedure:--- (deletion of TAMIP diacetate, containing kieselgur, can also be used)

6. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: TAMIP-diacetate: Manufacturing procedure:[….]---

A: TAMIP-diacetate: Manufacturing procedure: [….] 3 Alternatively sulfuric acid, conc. or dilutions prepared from them may also be used.

7. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

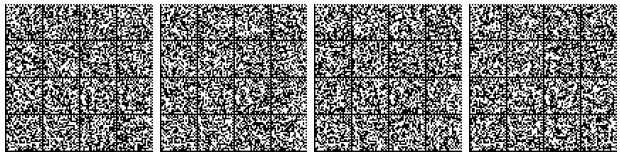
Da: TIP diamide chloride: Yield: 1638 to 1998 kg Of theory: 81 to 99 %

A: TIP diamide chloride: Yield: 2281 to 2805 kg Of theory: 81 to 100 %

8. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: Iopromide crude: 4 During distillation the concentrate of the activated charcoal washings of iopromide, pure can be added and if appropriate after the addition of water, purified the filter substance from the drying of iopromide, pure can be added.

A: Iopromide crude: 5 After the addition of water the filter substance from the drying of iopromide, pure can be added. Instead of water product containing solutions arising from the Iopromide, crude, purified and pure steps can also be used. A total amount of approx. 200 kg



Iopromide can be transferred back within the process via the described ways.

9. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: Iopromide purified: 3 The iopromide, purified eluate from 4 cycles can be combined and concentrated.

A: Iopromide purified: 3 the iopromide, purified eluate from up to 4 cycles can be combined and concentrated.

10. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: Iopromide pure: Manufacturing procedure: Fill in the first part of the concentrated iopromide, purified and check the clarity of the solution. While stirring, adjust with water to a density of 1.220 to 1.320 g/ml and a mass of 2640 to 3300 kg and determine the conductivity and pH (required conductivity: < 50 µS/cm, required pH = 6.0 to 7.3). [...] Repeat the procedure analogously with the second part of the concentrated iopromide, purified. [....]

A: Iopromide pure: Manufacturing procedure: Fill in the concentrated iopromide, purified and check the clarity of the solution. Adjust with water to a density of 1.220 to 1.320 g/ml and determine the conductivity and pH (required conductivity: < 50 µS/cm, required pH = 6.0 to 7.3).

11. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: Iopromide pure: Manufacturing procedure: Separate off the activated charcoal and then wash with water followed by pure acetone and water again, in that order.

A: Iopromide pure: Manufacturing procedure: Separate off the activated charcoal and then wash with water followed by acetone [5] and water again, in that order. 5 Alternatively recycled acetone can be used.

12. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: Iopromide pure: Manufacturing procedure: Requirement (Karl Fischer method): ≤ 0.8% and stir the suspension for at least six hours at 60 to 70 °C.

A: Iopromide pure: Manufacturing procedure: Requirement (Karl Fischer method) [8]: ≤ 0.8 % and stir the suspension for at least six hours at 60 to 70 °C. 8 Alternatively NIR can be used to determine the water content.

13. Variazione Tipo IB n. 10 – Modifica minore del processo di produzione del principio attivo

Da: Iopromide pure: Manufacturing procedure: Dry the crystal material at max. 80 °C until the water content is 1 % and the ethanol content is 0.4 %. Transfer the substance to polyethylene bags in fiber drums.

A: Iopromide pure: Manufacturing procedure: Dry the substance at max. 80 °C for at least 6 hours.

I lotti già prodotti sono mantenuti in commercio fino alla data di scadenza indicata in etichetta ai sensi dell'art. 14 D.L.vo 178/91 e successive modificazioni ed integrazioni.

Decorrenza della modifica: dal giorno successivo alla data della sua pubblicazione in Gazzetta Ufficiale.

Un procuratore dirigente Dr. Salvatore Lenzo

TS-09ADD3620 (A pagamento).