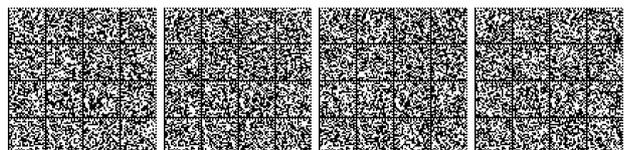


IPC1: pH may be adjusted at this stage	<b>Mix.</b> IPC3: pH measurement
Step 5 In line filtration with 0.2 µm membrane cartridges. IPC2: Control of filters	Step 12 Filter the solution using 0.22 µm membrane cartridges.
Step 6 Packaging. IPC3: Analytical control IPC4: Filling volume IPC5: Packaging compliance	Step 13 Fill and Pack. IPC4: <b>Density</b> IPC5: Average fill volume IPC6: Packaging compliance

variazione B.II.b.4 z) - Tipo IB unforeseen - modifica della dimensione e della formulazione del lotto\*

MANUFACTURING FORMULA PRESENT			MANUFACTURING FORMULA PROPOSED	
DA			A	
Section II.B.1			Module 3.2.P.3.2	
Manufacturing formula			Batch formula	
			The typical batch sizes for Actigrip Gola are: <b>67,390 litres for the continuous process</b> 10,000 litres for the batch process	
Manufacturing formula for continuous process			Manufacturing formula for continuous process	
Typical batch size: 100,000 litre or 60,000 litre. Each 10,000 litre of concentrate provides 100,000 litre of finished product, after dilution.			The typical batch size for the concentrate is 10,000 litres which, after dilution, provides <b>67,390 litres of finished product.</b> <b>The ratio of dilution is 1 litre of concentrate for 6.739 litres of diluted finished product.</b>	
Each 6,000 litre of concentrate provides 60,000 litre of finished product, after dilution.				
Ingredient	10,000 l of concentrate	6,000 l of concentrate	Ingredient	10,000 l of concentrate
Hexetidine	100.000 kg	60.000 kg	Hexetidine	67.39 kg
Polysorbate 60	700.000 kg	420.000 kg	Polysorbate 60	471.73 kg
Citric Acid Monohydrate (1)	41.800 kg	25.080 kg	Citric Acid Monohydrate	28.17 kg
Saccharin Sodium	22.000 kg	13.200 kg	Saccharin Sodium	14.83 kg
Azorubin (85%) (E122) (2)	2.300 kg	1.380 kg	Azorubin (85%) (E122) (1)	1.55 kg
Methylsalicylate	18.600 kg	11.160 kg	---	---
Levomenthol	18.600 kg	11.160 kg	Levomenthol	47.17 kg
Peppermint Oil	64.000 kg	38.400 kg	---	---
Anise Oil	39.250 kg	23.550 kg	---	---
Eucalyptus Oil	1.100 kg	0.660 kg	Eucalyptus Oil	0.741 kg
Clove Oil	8.450 kg	5.070 kg	---	---
---	---	---	Sodium Calcium	67.39 kg



			Edetate	
<b>Ethanol 96%</b>	4,333.333 kg	2,600.000 kg	<b>Ethanol 96%</b>	2920.01 kg
---	---	---	Sodium Hydroxide	qs pH 5.5 ± 0.2
<b>Purified Water</b>	<b>3,940.567 kg</b>	<b>2,364.340 kg</b>	<b>Purified Water</b>	qs 10,000 l
1) Batch quantity may be adjusted ± 10% to obtain a pH within 4.7 - 5.1 (2) Batch quantity adjusted according to the titre (theoretical titre 85%)			(1) Batch quantity adjusted according to the potency (theoretical potency 85%)	
Manufacturing Formula for 100,000 litre of finished product from 10,000 litre of Concentrate: Actigrip Gola concentrate 10,000 l: 9,290.000 kg Purified water q.s. 100,000 l: 89,810.000 kg				
Manufacturing Formula for 60,000 litre of finished product from 6,000 litre of Concentrate: Actigrip Gola concentrate 6,000 l: 5,574.000 kg Purified water q.s. 60,000 l: 53,886.000 kg				
<b>Manufacturing formula for batch process</b>			<b>Manufacturing formula for batch process</b>	
Typical batch size: 10,000 litre <del>or 6,000 litre</del> . Each 1,000 litre of concentrate provides 10,000 litre of finished product, after dilution. Each 600 litre of concentrate provides 6,000 litre of finished product, after dilution.			The typical batch size is 10,000 litres.	
<b>Ingredient</b>	<b>1,000 l of concentrate</b>	<b>600 l of concentrate</b>	<b>Ingredient</b>	<b>Batch size 10,000 l</b>
<b>Hexetidine</b>	10.000 kg	6.000 kg	<b>Hexetidine</b>	10.00 kg
<b>Polysorbate 60</b>	70.000 kg	42.000 kg	<b>Polysorbate 60</b>	70.00 kg
<b>Citric Acid Monohydrate (1)</b>	4.180 kg	2.508 kg	<b>Citric Acid Monohydrate</b>	4.18 kg
<b>Saccharin Sodium</b>	2.200 kg	1.320 kg	<b>Saccharin Sodium</b>	2.20 kg
<b>Azorubin (85%) (E122) (2)</b>	0.230 kg	0.138 kg	<b>Azorubin (85%) (E122) (1)</b>	0.23 kg
<del>Methyl Salicylate</del>	1.860 kg	1.116 kg	---	---
<b>Levomenthol</b>	1.860 kg	1.116 kg	<b>Levomenthol</b>	<b>7.00 kg</b>
<del>Peppermint Oil</del>	6.400 kg	3.840 kg	---	---
<del>Anise Oil</del>	3.925 kg	2.355 kg	---	---
<b>Eucalyptus Oil</b>	0.110 kg	0.066 kg	<b>Eucalyptus Oil</b>	0.11 kg
<del>Clove Oil</del>	0.845 kg	0.507 kg	---	---
---	---	---	Sodium calcium edetate	<b>10.00 kg</b>
<b>Ethanol 96%</b>	433.333 kg	260.000 kg	<b>Ethanol 96%</b>	433.30 kg
---	---	---	Sodium Hydroxide	qs pH 5.5 ± 0.2
<b>Purified Water</b>	<b>394.057 kg</b>	<b>236.434 kg</b>	<b>Purified Water</b>	qs 10,000 l
(1) Batch quantity may be adjusted ± 10% to obtain a pH within 4.7 - 5.1. (2) Batch quantity adjusted according to the titre (theoretical titre 85%)			(1) Batch quantity adjusted according to the potency (theoretical potency 85%)	



<p><b>Manufacturing Formula for 10,000 litre of finished product from 1,000 litre of Concentrate:</b>                  Actigrip Gola concentrate 1,000 l: 929.000 kg                  Purified water q.s. 10,000 l: 8,981.000 kg</p>	
<p><b>Manufacturing Formula for 6,000 litre of finished product from 600 litre of Concentrate:</b>                  Actigrip Gola concentrate 600 l: 557.400 kg                  Purified water q.s. 6,000 l: 5,388.600 kg</p>	

\*La modifica della *batch formula* è richiesta con l'AIN/2013/532.

variazione B.II.b.5 z) - Tipo IB unforeseen - modifica della frequenza dell'IPC controllo della dissoluzione

IPCs FREQUENCY PRESENT DA	IPCs FREQUENCY PROPOSED A
Section II.B.2	Module 3.2.P.3.3
Continuous process IPCs	Continuous process IPCs
	<b>Step 2</b> Control of dissolution: complete dissolution
	<b>Step 3</b> Control of dissolution: complete dissolution
Step 2 After stirring visual control: no droplet detected	Step 4 Control of dissolution: absence of oil droplets
Batch process IPCs	Batch process IPCs
	<b>Step 2</b> Control of dissolution: complete dissolution
<b>Step 1</b> After stirring visual control: no droplet detected	---
	<b>Step 5</b> Control of dissolution: complete dissolution

B.II.b.5.z) - Tipo IB unforeseen - modifica dell'IPC controllo del pH

DA	A
Section II.B.2	Module 3.2.P.3.3
Continuous process IPCs	Continuous process IPCs
Step 4 pH: 4.7 – 5.1	Step 11 pH: 5.5 ± 0.2
Batch process IPCs	Batch process IPCs
Step 4 pH: 4.7 – 5.1	Step 11 pH: 5.5 ± 0.2

B.II.b.5.z) - Tipo IB unforeseen - eliminazione di un metodo di analisi per l'IPC controllo continuo della diluizione (controllo dell'assorbanza)

DA	A
Section II.B.2	Module 3.2.P.3.3
Continuous process IPCs	Continuous process IPCs
Step 5 Continuous control of dilution May be performed by two ways: - control of the absorbance of the diluted product - continuous control of flow rates	Step 5 Continuous control of dilution May be performed by two ways: --- - continuous control of flow rate

B.II.b.5.c) - Tipo IA - eliminazione dell'IPC controllo dei filtri

