DRUG DEVELOPMENT

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Drug **D**evelopment & **M**anufacture for **P**harmaceutical **T**echnology **P**rofessions

GENERIC DRUG DEVELOPMENT

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GENERIC DRUG DEVELOPMENT SERIES

2002

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The World of Drug Development

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Company
Responsible Officer

_____

For and on behalf of the purchasing Company

[FAX OR MAIL BACK THIS PAGE BEFORE USE]

Jennifer Anne Slemment

Authorized signature of Locum International marketing director

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PRODUCT MASTER FORMULA

Generic Name: **Pseudoephedrine 60mg / Triprolidine 2.5mg Tablets**	**IAGIM**	Signatures ➲ Development	
	Edition No: 02	Validation ➲	
DEPARTMENT: Granulation & Tabletting	Edition Status: Spsds. 01	Production ➲	
PRECAUTION: Wear mask and gloves	Effective Date: **Jan/15/2002**	Q.A. ➲	
CAUTION: 1.Wear Masks with air filters 2.Potent Active Materials	Cat. No: **IAG-167-2000**	R.A. ➲	

CHANGE : No change

BATCH NO. _____ Weighing Date : _____

Per Unit Dose	Ex-cess	**Raw Materials** **300 000** units	**Per 91.220 Kg**					Signatures Weighing Depart.	
			kg	g	mg	L	mL	A	B
		PART I							
62.0		Lactose Monohydrate NF (200 mesh)	18	600					
2.5		Triprolidine HCl	0	750					
60.0	6.0	Pseudoephedrine HCl	19	800					
		PART II							
60.0		Starch NF	18	000					
		PART III							
90.0		Lactose Monohydrate NF (200 mesh)	27	000					
		PART IV							
-		Purified Water USP (85-95°C)	23	000					
2.3		PVP K-30 (Povidone USP)	0	690					
14.0	1.4	Starch NF	4	620					
		PART V							
-		Purified Water USP q.s. (up to 6.0 kg)	qs	000					
		PART VI							
5.6		Ac-Di-Sol™ (Croscarmellose Sodium NF)	1	680					
3.6		Magnesium Stearate NF	1	080					
300.0	7.4	Theoretical End Volume	**91**	**220**					

10% Excess Starch NF added to compensate the loss of water during the granulation/drying process

ED. N0: 02 Replaces 01	Effective Date:	**APPROVED:**			
Ed. Status : 02 - EU	Jan / 15 / 2002	Department	R&D	RA	QC / QA

Commercial Manufacturing Instructions

OUTLINE OF STANDARD OPERATING PROCEDURES FOR : MANUFACTURING AND PROCESSING

1. **Production Planning** - Prepares a production order file for each production batch according to the production schedule.
2. **Production Planning** - Assigns batch numbers, according to the existing code procedure, and enters these numbers in the batch numbers log.
3. **Production Planning** - A photocopy of the master formula record and manufacturing instructions is prepared with the specific manufacturing batch number.
4. **Production Planning** - Prepares all forms needed in the manufacturing process which are placed in the product order file.
   The file is then transferred to the Weighing Center/Dispensing Area.
5. **Dispensing Area** - Weighs all raw material components according to the master formula record. For each weighing, the raw material receiving logbook number is entered on the master formula record. All materials belonging to one manufacturing batch of the product is placed on a separate pallet and covered with a pallet cover or clear shrink-wrap.
   As per production schedule the pre-weighed raw material on pallets are transferred to productions, by production personnel, under the responsibility of the department head.
6. **Production Depts.** - During manufacturing, the product test results are recorded on the control forms which are attached to the master formula and manufacturing instructions batch record.
7. **Production Planning** - forwards a “Standard Packaging Sheet” with the computerized order to the packaging department.
8. **Packaging Department** - forwards the “Standard Packaging Sheet” and the computer order to the packaging materials warehouse.
9. **Packaging Department** - Authorizes packaging startup, in-process compliance, on the “Packaging Work Sheet”.
10. After packaging, the packaged goods are transferred to the warehouse/holding area under a quarantine status, pending QC release.
11. The product is tested by the QC analytical laboratory.
12. Production records and test results are analyzed by QA Department and on release the product is moved to the warehouse ready for shipment.
13. The batch records are archived by the Quality Assurance Department.
14. **Shipping Department** - maintains a complete and traceability record of the dispatches of each product batch number and its final destination.

Commercial Manufacturing Instructions

PRODUCTION YIELDS - SOP OUTLINE

Manufacturing format for the calculation of batch yield incorporates three different calculations. The first yield calculation is termed the “Usable % Yield”.
The second term “Overall % Yield” and the third calculation as Batch Yield. These three yield calculations differ as follows:

USABLE % YIELD:

This calculation is performed at the end of each step in the manufacturing process and is recorded within the actual *Manufacturing Procedure* documents. The intent of the calculation is to define the usable amount of material available for use in the next manufacturing step (i.e. compression, packaging, etc.). Because this value is only determining the “available” amount of material, it does not take into consideration the amount of material that may be lost to waste, sampling or rejection during compression/encapsulation/coating. Logically, this value is calculated for informational purposes and is not held to specific limits as it is partially dependent on sampling requirements and equilibration of manufacturing equipment (i.e. tablet presses, etc.).

OVERALL % YIELD:

This calculation is performed at the end of each step in the manufacturing process and is recorded on the attachment entitled *Material Balance/Dry Production*. The intent of the calculation is to determine the overall batch yield attained at each step in the process. Because this value determines the overall yield, it takes into account not only the “usable” portion of the batch but also the quantity of material lost to recoverable waste, sampling and rejection during compression/ encapsulation/ coating. Since this value incorporates all measurable and accountable quantities of the material, it is used as a means with which to control the manufacturing process. The limit established for this value is “Not less than 98% [in other words “not more than 2% unexplained loss”] from the previous manufacturing stage.” In the event that this limit is not achieved during the batch production, report of the deviation is made in an accompanying *Manufacturing Deviation Report*.

BATCH YIELD:

This calculation is performed after the completion of the entire manufacturing process and is also recorded on the attachment entitled *Material Balance - Dry Production*. The intent of this calculation is to determine the yield of the batch across the entire manufacturing process. Because this value determines the entire batch yield, it takes into account the final packaged quantity (converted into weight), as well as the quantities of recoverable waste, samples and rejections from each manufacturing stage.
Since this value also incorporates all measurable and accountable quantities of the material from an entire batch production view point, it is used as a yardstick with which to control the manufacturing process. The limit established for this value is “ 95.0% - 103.0%” [of the theoretical batch quantity].
In the event that this limit is not achieved at the end of the manufacturing process, report of the deviation and its resultant investigation is made in an accompanying *Manufacturing Deviation Report*.

Commercial Manufacturing Instructions

MANUFACTURING INSTRUCTIONS FOR COMMERCIAL PRODUCTION

Identification of Batch Parameters.

Product name: Pseudoephedrine HCl 60mg ; Triprolidine HCl 2.5 mg **Tablets**
Batch Number: [IAG167-07]
Department: Tablets
Batch Size: [300 000] units
Precautions: ① ②
Sub-lot No: 1
Caution:
Manufacture Date: Jan 25, 2000
Cat./Formula No: # ACT0167
Cores [✕] : Coated[✕] Tablets [✔]
Based on Validation: Batch # P0011
Validation Lot
Commercial Lot

Change Control for this document: Original - No Change ✔ : Change
Change made: - none

KEY:

Precautions: ①**Wear Mask and Gloves**
②**Wear disposable overalls**
Use air stream face visor with AIR filter
Use Mask, Gloves and Safety glasses

Caution: **Avoid exposure to light / Protect form light**
Store in well closed containers
Potential danger to pregnant women
Pregnant women prohibited in this area
Do not heat above 00øC
Room humidity below 30%

Special Note:

Manufacturing instructions.

Detailed manufacturing process for plain **scored tablets**

Commercial Manufacturing Instructions

MANUFACTURING INSTRUCTIONS FOR COMMERCIAL PRODUCTION

MANUFACTURING INSTRUCTIONS Pseudoephedrine HCl 60mg;Triprolidine HCl 2.5 mg **Tablets**	Machine No:	Sign	Sign	Date

1 Identify the equipment and verify the cleanliness prior to use.

PART ONE

2. ADD to (Diosna 500 / LOEDIGE 300 L) the ingredients from **PART I** strictly in the following order:

Lactose Monohydrate NF (200 mesh)
Triprolidine HCl
Pseudoephedrine HCl
and mix for [**3**] minutes at mixer speed **I** and Chopper **I** .

3. ADD to (Diosna 500 / LOEDIGE 300 L) the ingredient from **PART II**

Starch NF
and mix for [**3**] minutes at mixer speed **I** and Chopper **I**

4. ADD to [Diosna 800] the ingredient from **PART III**

Lactose Monohydrate NF (200 mesh)
and mix for [**3**] minutes at mixer speed **I** and Chopper **I**

GRANULATION SOLUTION PREPARATION

5 (i) Weigh [**23**] Kg PURIFIED WATER USP (85°C - 95°C) into a stainless steel vessel fitted with a roller mixer. (#1)
5 (ii) Operate the mixer and add the PVP K-30 (POVIDONE USP) and mix until fully dissolved.
5 (iii) While mixing, add the STARCH NF until a smooth paste is obtained

GRANULATION SOLUTION PREPARATION

6a. Add the granulating paste to the (Diosna 500 / LOEDIGE 300 L) while mixing at mixer speed **II** and chopper speed **II**.
Total Mixing Time is 35 seconds.

Time of adding Solution - [**5**] seconds
Time of mixing - [**30**] seconds

6b. If necessary, add the PURIFIED WATER USP (up to 6.0 kg). and/or mix at the same conditions as in stage 6. DO NOT OVERWET
Amount of additional PURIFIED WATER USP _____ Kg.
Additional mixing time [NMT 10] seconds _____ ____ Seconds

6c. Discharge the wet granulate to GLATT WSG-60 trolley while mixing at mixer speed **I**.
7a. Dry the wet granulate in the GLATT WSG-60 under the following settings:
Inlet Air Temperature NMT **60 - 70** ºC (Target: **65**ºC)
Outlet Air Temperature NMT **50**ºC (Target: **48**ºC)

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Commercial Manufacturing Instructions

MANUFACTURING INSTRUCTIONS FOR COMMERCIAL PRODUCTION

MANUFACTURING INSTRUCTIONS Pseudoephedrine HCl 60mg;Triprolidine HCl 2.5 mg **Tablets**	Machine	Sign	Date
7b Attach the temperature graph of the GLATT WSG-60 to the manufacturing instructions. Immediately add the batch number to the temperature graph and date and sign it. 8a. Mill about 1Kg. 'check portion' the dried granulate through a OSCILLATING GRANULATOR fitted with a [**1.0** mm] screen. 8b. Check the milled granulate portion for Loss on Drying (LOD). Use (Computrac / Mettler) IR machine with temperature set at temperature **105**º C Record First result: _____[0.0%] LOD Limits: [**1.6 to 2.5**%] 8c. If necessary, continue to dry the bulk granulate under the same conditions as stage 7, until the LOD is close to the midpoint of the given range limits and check moisture again. Record Second result: **[**_____**]** [**1.6 to 2.5**%] 8d. Pass the remainder of the dried granulate through the OSCILLATING GRANULATOR (**Frewitt**) fitted with a [**1.0** mm] screen into a [200] liter container or bin. 9. Weigh the milled granulate. **[**_____**]**Kg. Immediately add the batch number to the scale print-out, attach to the manufacturing instructions, date and sign the print-out. 10. Theoretical Weight [**88.46**] Kg. Yield **[**_____**]** % (Yield Limits: NLT 95% of Theoretical Weight.) Bins **[**_____**]** **PART TWO** 11. Transfer the milled granulate from stage 10 of both sub lots to a twin **shell blender / Flow bin (Y-Cone).** 12. Sieve the AC-DI-SOL (CROSCARMELLOSE SODIUM NF) through a **30** mesh screen sieve. 13. Transfer the sieved AC-DI-SOL™ (CROSCARMELLOSE SODIUM NF) and the MILLED GRANULATE from step 8 to a Y-CONE 120, and mix for **20** minutes 14. Sieve the MAGNESIUM STEARATE NF through a **50** mesh screen sieve, and transfer the sieved MAGNESIUM STEARATE NF to the mixture in the Y-CONE 120, and mix for **5** minutes Speed: [10.0] rpm. Mixing Start Time: **[**_____**]** Mixing Stop Time: **[**_____**]**			

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Commercial Manufacturing Instructions

MANUFACTURING INSTRUCTIONS FOR COMMERCIAL PRODUCTION

MANUFACTURING INSTRUCTIONS Pseudoephedrine HCl 60.0; Triprolidine HCl 2.5 mg **Tablets**	Machine	Sign	Date

PART THREE

15. Collect **10** samples, each equivalent to the approximate weight of one tablet (**300** mg) in labeled sample containers. Collect samples from upper, middle and lower part of the container. Send the samples to the QC laboratory for Blend Uniformity Testing.

16. Weigh the final blended material
Actual weight: [00.0] Kg.
Theoretical Weight [**91.22**] Kg. Yield **[9 .]** %
No. of containers **[_____]**
(Yield Limits: NLT 98% of **total** actual weight).

TABLETTING - COMPRESSION
17. Identify and verify the cleanliness of the tabletting equipment in use

Compress the final blend according to the written product specifications of weight, hardness and thickness
Tabletting machine: (**Kilian**).
Machine Speed 75 000 - 80 000 Tablets per hour
Limit of rpm NLT **[_____]** rpm ; NMT **[_____]** rpm

18. Weigh the tablets:
Actual production weight: **[_____]** Kg.
Weight of Samples taken: **[_____]** Kg.
Vacuum and rejects Weight: **[_____]** Kg.
Total weight **[_____]** Kg
No of Bulk Containers **[_____]**
Theoretical Weight **[_____]** Kg.
Yield **[_____]** %

(Yield Limits: NMT 2% unexplained loss compared to the final blend weight from stage 16.

19. Seal the double PE plastic bags (clear inner, black outer) with plastic ties then close all containers, and attach (bar coded) labels to the Bulk Containers for transport to the holding area.

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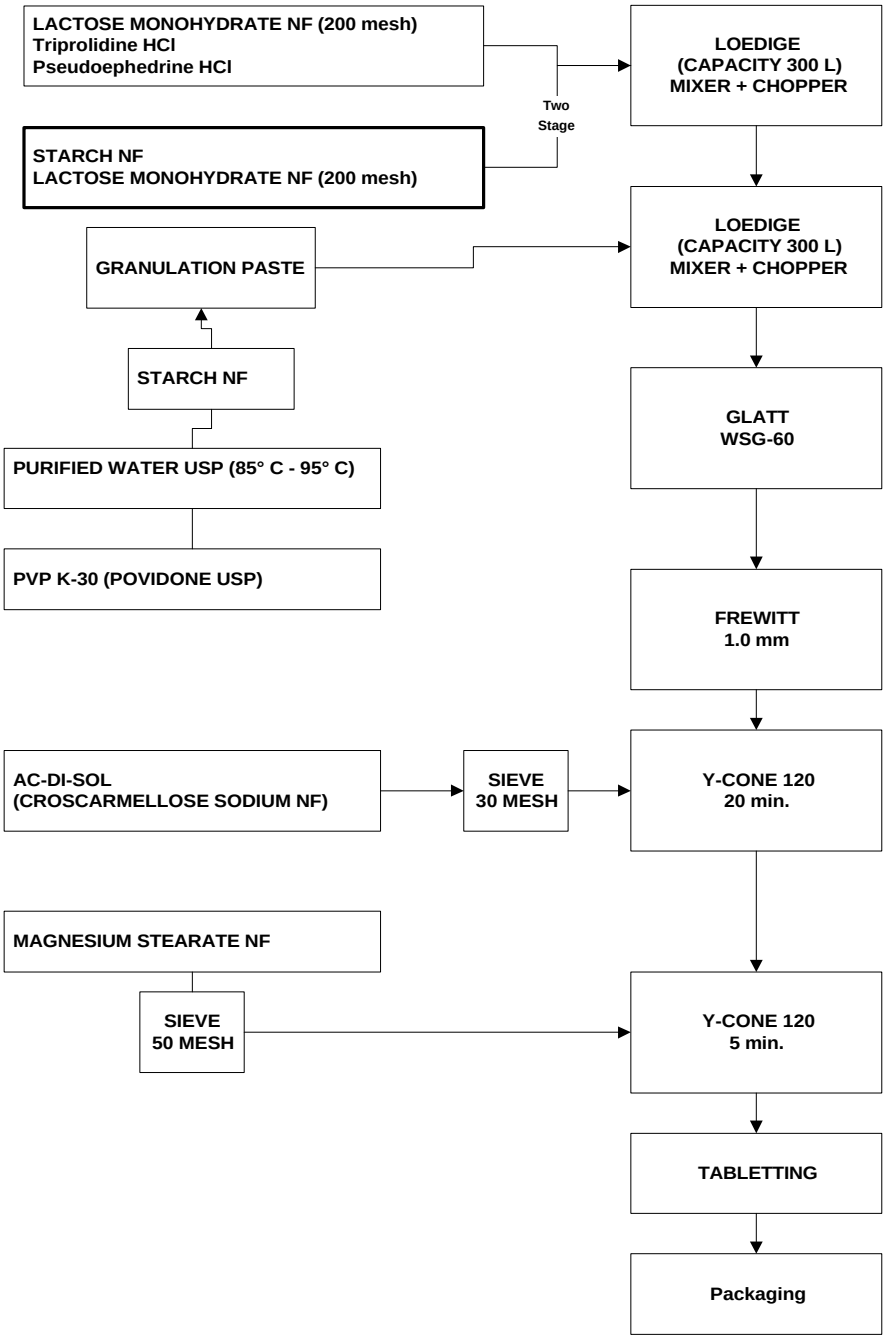
Commercial Manufacturing Instructions

Manufacture Procedure for Pivotal Batch

Flow Chart

Pseudoephedrine HCl 60.0; Triprolidine HCl 2.5 mg **Tablets**



Commercial Manufacturing Instructions

IN-PROCESS CONTROL SPECIFICATION

GRANULATION AND TABLETTING SUMMARY

FULL SIZE COMMERCIAL BATCH

Pseudoephedrine HCl 60.0; Triprolidine HCl 2.5 mg Tablets. Lot No: [0000]

Quantity [300 00] **MNF Date: Month DD, 200Y**

Dried Granulation Moisture Content	Limit: 1.6 - 2.5 %
Milled Granulation Yield	Limit: NLT 98.0%
Total Final Blend Yield	Limit: NLT 98.0% (based on actual quantities processed).
In-Process Final Blend Uniformity	Limit: 94.0 - 106.0% of labeled amount RSD ≤ 6.0% (as per attached specifications)
Tabletting Yield	NMT 2.0% unexplained loss from the previous final blend step.
Overall Production Yield	NLT 95.0%

[1] Recorded on Statistical Data Work Sheets.

Blend Uniformity

The requirements for Blend Uniformity are met if the amount of the active ingredient in each of the 10 samples, as determined from the Blend Uniformity Analytical Method, lies within the range of 90.0 - 110.0% of the labeled amount and the Relative Standard Deviation is less than or equal to 6.0%.

If 1 sample is outside the range of 90.0 - 110.0% of labeled amount and no sample is outside the range of 80.0 - 120.0% of labeled amount, or if the Relative Standard Deviation is greater than 6.0%, or if both conditions prevail, test 20 additional samples.

The requirements are met if not more than 1 sample of the 30 is outside the range of 90.0 - 110.0% of labeled amount and no sample is outside the range of 80.0 - 120.0% of labeled amount, the Relative Standard Deviation of the 30 samples does not exceed 7.8%.

CommercialManufacturing Instructions

IN-PROCESS CONTROL SPECIFICATION - TABLET CORES

SUMMARY

PROPOSED FULL SIZE COMMERCIAL BATCH

Pseudoephedrine HCl 60.0; Triprolidine HCl 2.5 mg **Tablets**.

In-process Specifications for cores.

Punch Diameter	9.10 mm
Punch No	[23a]
Die No.	[23b]
Description	[Color] (white to off-white) round tablet
Scoring	[scored on **one** side]
Core Diameter	Nominal 9.1 Limit: 9.0 - 9.2 mm
Individual Unit weight (±7.5%)	Nominal 300.0 Limit: 000.0 - 000.0 mg:
Average Unit weight (±5.0%)	Nominal 300.0 Limit: 000.0 - 000.0 mg:
Thickness	Nominal 4.2 Limit: 3.8 - 4.8 mm
Hardness	Target: 10 SCU NLT 7.0 - NMT 14 SCU.
Friability	NMT 1.0 %