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(Ann I)



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Kala-azar Elimination Programme,  
NVBDCP, India  
Dr. Chusak Prasittisuk, WHO-SEARO,  
New Delhi  
Dr. J. Karbwang, WHO/TDR, Geneva

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Your Reference

Our Reference

Direct Dial  
(069) - 426 02 - 3429

Date  
29 July 2005

**Technical information about Miltefosine/Impavido(R): Drug substance and drug product**

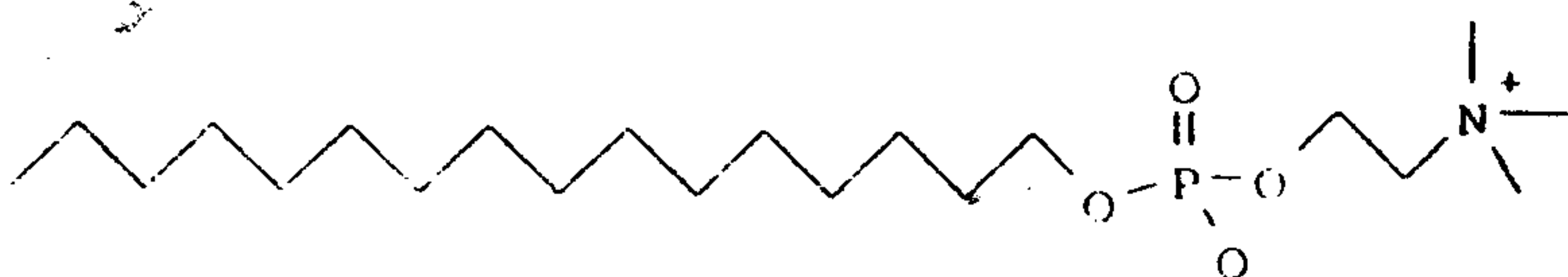
Ladies and gentlemen,

Referring to different requests please find below a summary of technical data on miltefosine/Impavido. As no specific details were requested we have compiled the information that we feel should be most relevant. In case of missing details that you may need, we will try to provide these at short notice.

1. Summary of characteristics of Miltefosine drug substance , current specifications and shelf-life

Characteristics:

Chemical structure



Chemical name

International non-proprietary name (INN): Miltefosine

IUPAC name:  
trimethylammonium inner

2- [ [ (Hexadecyloxy)hydroxyphosphenyl] oxy] -N,N,N-  
complex salt

Synonym:

Hexadecylphosphocholin

Abbreviations:

HDPC, He-PC, HPC, MIL

Laboratory code:

D-18506

CAS-number:

58066-85-6

Storage: Miltefosine is hygroscopic and has to be stored in well closed containers protected from humidity

Safety:

swallowing must be avoided (protective

Contact with mucous membranes, inhaling and  
clothing)

## Current Specification

Test No.	Test	Specification
1.	Description	White, crystalline powder
2.	Identity	
2.1	IR-spectrum	IR spectrum must conform with standard IR spectrum
2.2	Point of decomposition	between 244 and 253 °C
3.	Purity	
3.1	Water content (Karl-Fischer)	not more than 4.5 %
3.2	Clarity and opalescence of the solution (1% in water)	not more than 3 FTU
3.3	Absorption at 400 nm (1% in methanol)	not more than 0.03
3.4	TLC purity:	
	1-n-Hexadecanol, choline and phosphorylcholine	not more than 0.1 % of each
	Sum of known impurities	not more than 0.3 %
	Unknown impurities, each	not more than 0.1 %
	Sum of unknown impurities	not more than 0.5 %
	Sum of known and unknown impurities	not more than 0.8 %
3.5	GC residual solvents	
	Ethylmethylketone or 2-Propanol	not more than 50 ppm
	Acetone	not more than 500 ppm
	Ethanol	not more than 500 ppm
	1-Butanol	not more than 50 ppm
	pH value (1% aqueous solution)	between 5.0 and 8.0
	Heavy metals (Ph.Eur.)	not more than 10 ppm
4.	Assay	
	Content related to the anhydrous substance (alkalimetrically with HClO <sub>4</sub> )	98.0 – 102.0 %

## Stability

The drug substance is stable over a period of 5 years if stored under temperatures < 30°C under dry conditions and in tightly closed containers.

2. Summary of composition, specifications and stability informations for Miltefosine 10 and 50 mg capsules

2a) 10 mg Miltefosine-Capsules

1 hard gelatine capsule 10 mg Miltefosine contains:

<b>Miltefosine</b>
Aerosil V 200 (silica, colloidal anhydrous)
Avicel PH 101 (cellulose, microcrystalline)
<b>Lactose Monohydrate</b>
Talc
<b>Magnesium-stearate V</b>

Current Release-Specification:

Test No.	Test	Specification
1.	<b>Description</b>	
	<i>Capsules</i>	Hard gelatine capsules
	<i>Size of capsules</i>	3
	<i>Colour of capsules</i>	Cap and body: opaque red
	<i>Contents</i>	White powder
2.	<b>Identity</b>	
	<b>Miltefosine (TLC)</b>	Positive
	<b>Iron oxide (E172)</b>	Positive
	<b>Titanium oxide (E171)</b>	Positive
3.	<b>Properties</b>	
	<i>Filling of the individual capsules</i>	Contents of 20 capsules; 18 of the individual weights must not deviate by more than 10 %, none to deviate by more than 20 % from the average weight.
	<i>Average filling weight</i>	140.0 mg $\pm$ 3.5% (135.0 – 145.0 mg)
	<i>Disintegration time</i>	Less than 15 minutes
4.	<b>Assay (TLC)</b>	
	<b>Miltefosine</b>	95.0 – 105.0 % (= 9.5 – 10.5 mg)
	<b>Content uniformity Miltefosine</b>	85.0 – 115.0 % (= 8.5 – 11.5 mg) rsd = $\leq$ $\pm$ 6.0 %
5.	<b>Purity (TLC)</b>	
	<b>1-Hexadecanol</b>	Not more than 0.2 %
	<b>Unknown individual impurity</b>	Each, not more than 0.2 %
	<b>Sum of impurities</b>	Not more than 1.0 %
6.	<b>Dissolution of the Active Ingredient</b>	
	<b>Miltefosine After 30 minutes</b>	More than 75.0 % of the declared content

## 2b) 50 mg Miltefosine-Capsules

1 hard gelatine capsule 50 mg Miltefosine contains:

Miltefosine
Aerosil V 200 (silica, colloidal anhydrous)
Avicel PH 101 (cellulose, microcrystalline)
Lactose Monohydrate
Talc
Magnesium-stearate V

## Current Release-Specification:

Test No.	Test	Specification
1.	<b>Description</b>	
	<i>Capsules</i>	Hard gelatine capsules
	Size of capsules	2
	<i>Colour of capsules</i>	Cap and body: opaque red
	Contents	White powder
2.	<b>Identity</b>	
	Miltefosine (TLC)	Positive
	Iron oxide (E 172)	Positive
	Titanium oxide (E 171)	Positive
3.	<b>Properties</b>	
	Filling of the individual capsules	Contents of 20 capsules; 18 of the individual weights must not deviate by more than 10 %, none to deviate by more than 20 % from the average weight.
	Average filling weight	190.0 mg $\pm$ 3 % (184.0 – 196.0 mg)
	Disintegration time	Less than 15 minutes
4.	<b>Assay (TLC)</b>	
	Miltefosine	95.0 – 105.0 % (= 47.5 – 52.5 mg)
	Content uniformity Miltefosine	85.0 – 115.0 % (= 42.5 – 57.5 mg) rsd = $\leq$ $\pm$ 6.0 %
5.	<b>Purity (TLC)</b>	
	1-Hexadecanol	Not more than 0.2 %
	Unknown individual impurity	Each, not more than 0.2 %
	Sum of impurities	Not more than 1.0 %
6.	<b>Dissolution of the Active Ingredient</b>	
	Miltefosine After 30 minutes	More than 75.0 % of the declared content

## 2b) 50 mg Miltefosine-Capsules

1 hard gelatine capsule 50 mg Miltefosine contains:

Miltefosine
Aerosil V 200 (silica, colloidal anhydrous)
Avicel PH 101 (cellulose, microcrystalline)
Lactose Monohydrate
Talc
Magnesium-stearate V

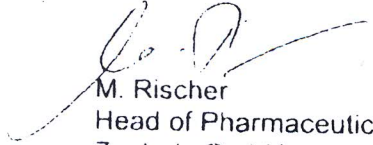
## Current Release-Specification:

Test No.	Test	Specification
1.	<b>Description</b>	
	<i>Capsules</i>	Hard gelatine capsules
	Size of capsules	2
	<i>Colour of capsules</i>	Cap and body: opaque red
	Contents	White powder
2.	<b>Identity</b>	
	Miltefosine (TLC)	Positive
	Iron oxide (E 172)	Positive
	Titanium oxide (E 171)	Positive
3.	<b>Properties</b>	
	Filling of the individual capsules	Contents of 20 capsules; 18 of the individual weights must not deviate by more than 10 %, none to deviate by more than 20 % from the average weight.
	Average filling weight	190.0 mg $\pm$ 3 % (184.0 – 196.0 mg)
	Disintegration time	Less than 15 minutes
4.	<b>Assay (TLC)</b>	
	Miltefosine	95.0 – 105.0 % (= 47.5 – 52.5 mg)
	Content uniformity Miltefosine	85.0 – 115.0 % (= 42.5 – 57.5 mg) rsd = $\leq \pm$ 6.0 %
5.	<b>Purity (TLC)</b>	
	1-Hexadecanol	Not more than 0.2 %
	Unknown individual impurity	Each, not more than 0.2 %
	Sum of impurities	Not more than 1.0 %
6.	<b>Dissolution of the Active Ingredient</b>	
	Miltefosine After 30 minutes	More than 75.0 % of the declared content

**Stability**

For both products a shelf-life of 5 years could be claimed if stored in the alu/alu-Blister up to 30°C

Sincerely yours,



M. Rischer  
Head of Pharmaceutical Development  
Zentaris GmbH



H. Sindermann  
Head of Clinical Research  
Zentaris GmbH

No. 12-104/96-DC

From  
Directorate General of Health Services  
Drugs Controller General (I)

Nirman Bhawan, New Delhi  
Dated :

22 AUG 2005

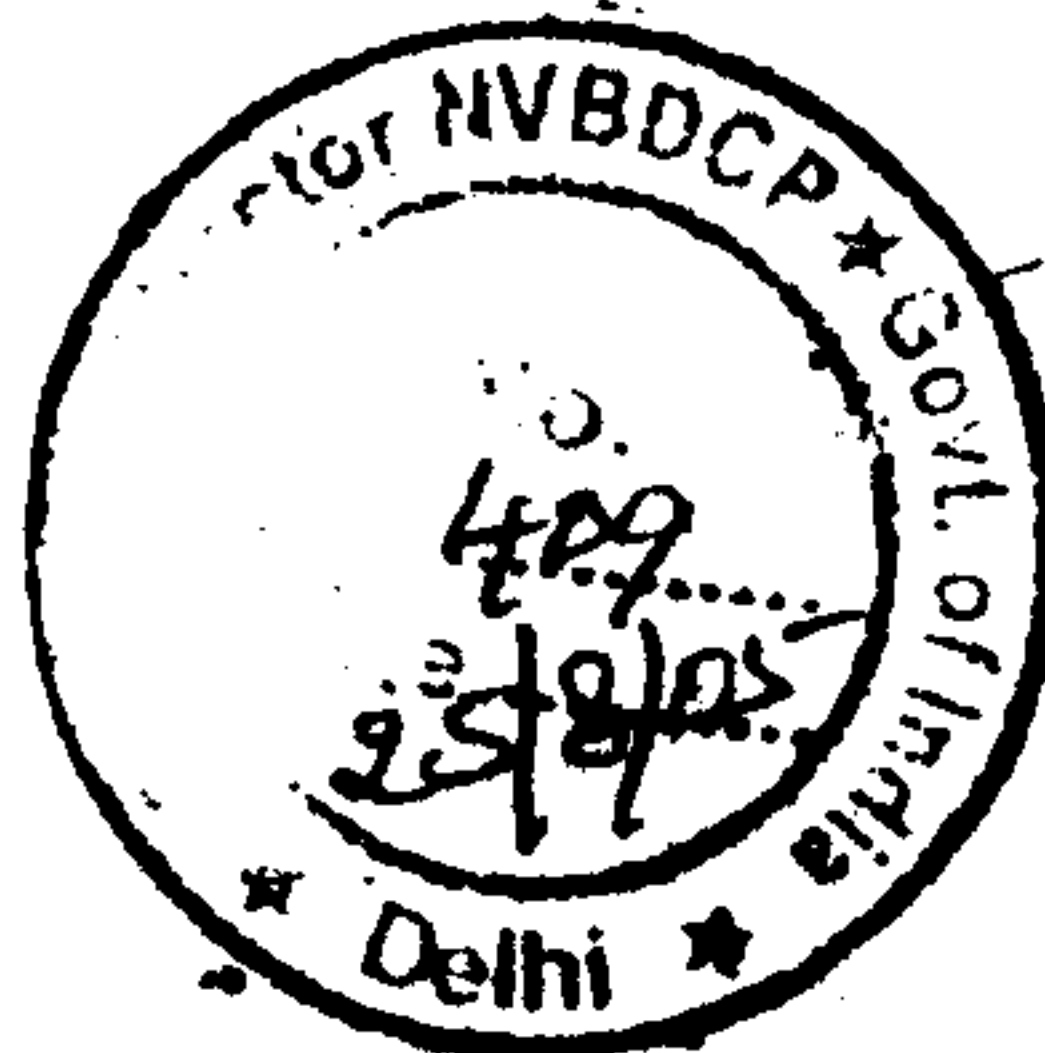
To  
The Joint Director & Programme Manager  
Kala azar Control,  
Directorate of National Vector Borne Disease Control Programme,  
22-Shamnath Marg,  
Delhi-110 054

Sub: Specifications for miltefosine - regarding.

Ref : Your letter no.3-55/2005-NVBDCP(KA) Miltefosine

Sir,

Please find enclosed a copy of specifications of  
miltefosine 10mg & 50mg capsules as requested by you.  
Hope this will meet your requirement.



Yours faithfully,  
*(Signature)*  
( A.B.Ramteke )  
For Drugs Controller General (I)

JDC (PKS)

Recd on 30/8

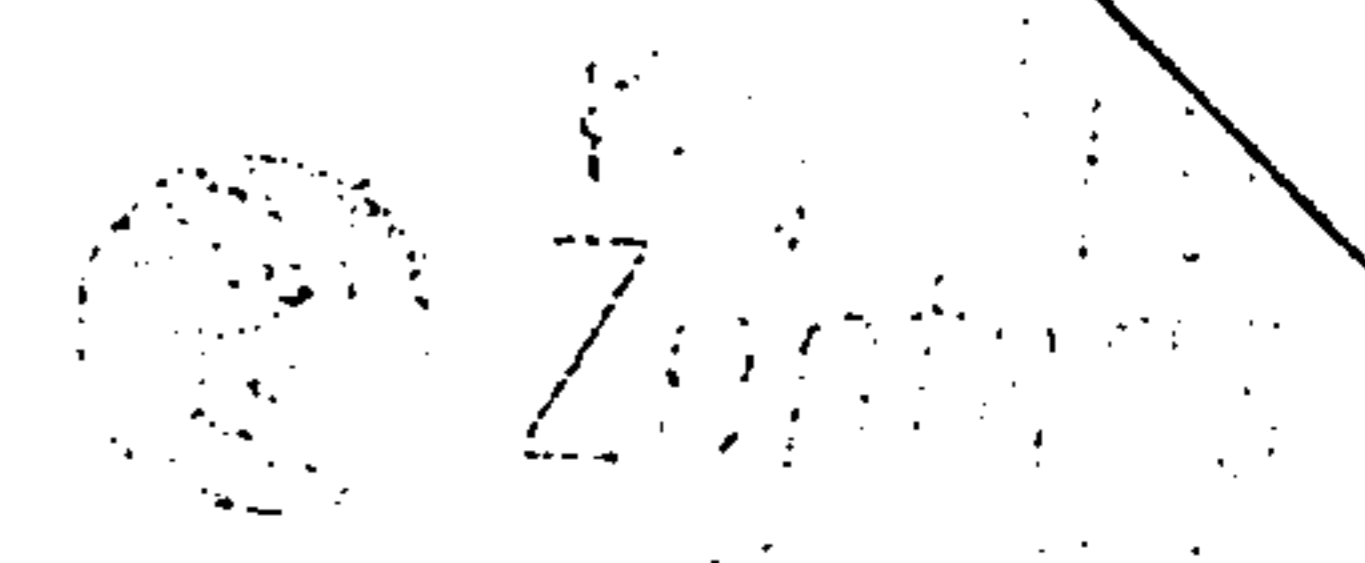
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JDC (PKS)

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REPORT

Date: July 16<sup>th</sup>, 2001

Project no.: D-18506 Project: Miltefosine  
 (INN):

Doc. Code (CTD): P 5.1

Report no.: D-18506/1200\_0057\_03(internal)

GMP Code: Z-PEZ-FS\_0057\_03(internal)

Title: Release Specification  
 Miltefosine 10 mg Capsules  
 3<sup>rd</sup> Ed.

Study Director: Dr. R. Martens

Study facility: Zentaris, Frankfurt am Main, GERMANY

KIND ATTENTION  
 MR VIJ  
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 DR R. H. JAMES

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Approved by:  Head of Pharmaceutical  
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