"Analysis of purity in 19 drug product tablets containing clopidogrel : 18 copies versus the original brand"

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Purity testing of the c1opidogre1 tab1ets at time point zero and after 3 months at 40°C and a relative humidity of 75%

Samp1eP	Product	Hydro1ysis product (%)		R-enantiomer (%)		Tota1 impurities (%)	
		Time O	3 months	Time O	3 months	Time O	3 months
Ref. batch 1	PLAVIX@a	0.04	0.29	0.24	0.35	0.56	1.71
Ref. batch 2	PLAVIX@a	0.04	0.32	0.25	0.31	0.65	1.84
Ref. batch 3	PLAVIX@a	0.04	0.33	0.25	0.40	0.61	1.69
1	P1agri1 75@	0.45	0.46	1.09	1.14	1.76	3.29
2	Clodre1@	0.85	1.36	2.24	3.61	3.55	5.55
3	Orawis@	0.67	1.36	0.57	3.30	1.52	5.21
4	Nok1ot@	0.86	1.35	1.71	2.70	2.97	4.85
5	C1opigre1@	0.15	1.40	5.68	6.12	6.65	9.71
6	Preva@	0.57	2.54	1.97	5.30	3.07	10.84
7	Clavix@	1.46	2.06	0.67	6.50	3.13	11.21
8	C1opilet@	<0.01	0.45	0.87	1.26	4.48	5.17
9	Stromix@	0.07	0.70	3.41	3.63	8.87	9.17
IO	Cloplat 75@	1.36	2.47	3.20	3.56	5.99	8.53
Il	Deplatt@	0.08	0.08	0.95	1.03	1.68	2.54
12	Ceruvin 75@	0.23	0.41	1.50	1.55	2.50	3.46
13	Clop1atic@	1.47	2.20	1.93	3.70	5.88	9.08
14	Plagre1@	0.21	0.26	0.79	0.80	1.78	1.90
15	Nefazan@	0.07	0.07	0.93	0.98	1.28	1.91
16	Ta1com@	0.04	0.08	1.11	1.68	2.46	3.43
17	C1opifran@	0.07	0.70	1.13	4.65	3.90	5.60
18	C1opigre1@	0.17	1.78	1.03	3.66	2.59	7.40

Tab 2

a Marketed as ISCOVER@ in some countries

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Analysis of purity in 19 drug product tablets containing clopidogrel : 18 copies versus the original brand

Overview of the samples used in this study and results for content

Sample	Product	Pharmaceutical Company (Country of origin)	Mean (% of Label laim(a)
Ref. batch 1	PLAVrx@b	Sano -Synthelabo (France)	97.2
Ref. batch 2	PLAVrx@b	Sano -Synthelabo (France)	99.3
Ref. batch 3	PLAVrx@b	Sano -Synthelabo (France)	97.3
1	Plagril 75@	Dr. Reddy's Laboratories Ltd. (India)	95.1
2	Clodrel@	Unichem Laboratories Ltd. (India)	88.7
3	Orawis@	Merck (India)	95.6
4	Noklot@	Zydus Medica (India)	91.6
5	Clopigrel@	USV Ltd. (India)	91.6
6	Preva@	Intas Pharmaceuticals Ltd. (India)	93.3
7	Clavix@	Intas Suprima (India)	93.6
8	Clopilet@	Sun Pharmaceutical Ind. Ltd. (India)	91.3
9	Stromix@	Nicholas Piramal (India)	86.5
10	Cloplat-75@	IPCA Laboratories Ltd. (India)	95.9
11	Deplatt@	Torrent Pharmaceutical Ltd. (India)	96.7
12	Ceruvin 5@	StancarelReddy (India)	96.1
13	Cloplatic@	Haymann (Uruguay)	90.3
14	Plagrel@	Servirnedic (Uruguay)	102.3
15	Nefazan@	Laboratorios Phoenix (Argentina)	96.4
16	Talcom@	Shenzen Salubris (Xi Lin Tai) (China)	94.5
17	Clopifran@	Laboratorios Lufra Farmacos S.A. (Dominican Rep.)	95.3
18	Clopigrel@	Noas Farma Uruguay S.A (Uruguay)	97.7

a) The dose is 75 mg expresed as clopidogrel base for all products except for sample 16 (Talcom@, China) having a dose of 25 mg

b) Marketed as ISCOVER@ in some countries.

Conclusion

A high level of impurities was found in many copies; over 60% of the copies contained more than four times the amount of hydrolysis product or R-enantiomer compared to the reference drug product. In addition, 50 % of the samples did not comply with the 95-105% limits for content.

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TICLOPIDINA CLORIDRATO

N° Ident.	Companies	Name of product
1	SANOFI-SYNTHELABO	TIKLID
2	ANGELINI	TICLOPIDINA ANGENERICO
3	DOC	TICLOPIDINA DOC
4	DOROM	TICLOPIDINA DOROM
5	EG	TICLOPIDINA EG
6	HEXAN	TICLOPIDINA HEXAN
7	MERCK GENERICS	TICLOPIDINA MG
8	PLIVA PHARMACEUTICAL	TICLOPIDINA PLIVA
9	RATIOPHARM	TICLOPIDINA RATIOPHARM
10	ERREKAPPA	TICLOPIDINA RK
11	TEVA	TICLOPIDINA TEVA
12	UNION HALTH	TICLOPIDINA UNION HALTH
13	PIAM	ANTIGREG
14	ROTTAPHARM	APLAKET
15	FARM. CABER	CLOX
16	B & G	FLUILAST
17	FARMAC. DAMOR	FLUPID
18	CHIESI PHARM.	KLODIN
19	GIENNE PHARM.	OPTERON
20	SIGMA TAU	TICLODONE

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TICLOPIDINA CLORIDRATO

Producer	Number of products
OMICRON PHARMA	5
IBN SAVIO	4
DOPPEL	3
SPECIAL PRODUCT'S LINE	3
CONS. F.CO BIOT. BIOPROGRESS	2
VARIE (n. 13)	1

CEP (EDQM)

TICLOPIDINE HYDROCHLORIDE

Certificate Holder	Certificate no.
ERREGIERRE (I)	081-1999
SANOFI CHIMIE (F)	052-2000
TEVA (I)	379-2001
POLI (I)	414-2001
USV (IND)	039-2002
AARTI DRUGS (IND)	116-2002
SIMS (I)	106-2002
RPG LIFE (IND)	066-2003

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RICHIESTE C P A

EMEA / EDQM

- Regole sull'approvazione DMF
- Modus operandi delle visite ispettive
- Formazione degli ispettori

VISITE IMPIANTI E APPROVAZIONE DMF CORRELATI

ALL'AIC CORRISPONDENTE

TEMPO LIMITE : 30 OTTOBRE 2005

OBBLIGO DI IDENTIFICAZIONE DEL NOME DEL PRODUTTORE API E DEL PAESE D'ORIGINE SULLA CONFEZIONE DEL FARMACO

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