Summary of Product Characteristics

Lamivudine/Zidovudine Tablets 150 mg/300 mg

1. NAME OF THE MEDICINAL PRODUCT

Lamivudine/Zidovudine Tablets 150 mg/300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg lamivudine and 300 mg zidovudine. For excipients see 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, film-coated, capsule-shaped, biconvex tablet debossed with 'M' on one side of the score and '2' on other side of score on one side of the tablet and 'L' on one side of the score and 'Z' on other side of the score on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lamivudine/Zidovudine Tablets 150 mg/300 mg is indicated in combination with another antiretroviral agent for the treatment of human immunodeficiency virus (HIV) infection in adults, adolescents and children weighing over 25 kg.

Consideration should be given to official treatment guidelines for HIV-1 infection (e.g. those of the WHO). For use of antiretroviral agents for post-exposure prophylaxis consult the most recent official guidelines, e.g. those of the WHO.

4.2 Posology and method of administration

Oral use.

Therapy should be initiated by a health care provider experienced in the management of HIV infection.

Adults, adolescents and children (weighing at least 25 kg):
The recommended dose of Lamivudine/Zidovudine Tablets 150 mg/300 mg is one tablet twice a day, approximately every 12 hours (see section 4.4).

Children weighing less than 25 kg
This product is not suitable for children weighing less than 25 kg because it cannot be given at the correct dose. For these patients, other formulations should be used, e.g. a tablet which contains a smaller amount of lamivudine and zidovudine.

Lamivudine/Zidovudine Tablets 150 mg/300 mg may be taken with food or between meals.

To ensure that the patient takes the entire dose, the tablet should be swallowed whole. For patients who cannot swallow tablets, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

Note. Where discontinuation of one of the active substances of Lamivudine/Zidovudine Tablets 150 mg/300 mg is necessary, or the dose needs to be adjusted, lamivudine and zidovudine preparations can be given separately. They are available as tablets and oral solutions.

Elderly
Special care is advised in the elderly because of age-associated changes such as decrease in renal function and alteration of haematological parameters.

Renal impairment
Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance ≤ 50 ml/minute), it is recommended that separate preparations of lamivudine and zidovudine are used (see section 4.4).

Hepatic impairment
Data from patients with moderate to severe hepatic impairment show that hepatic dysfunction does not affect lamivudine pharmacokinetics significantly. However, limited data in patients with cirrhosis suggest that zidovudine may accumulate in patients with hepatic impairment because of decreased glucuronidation. As zidovudine doses may need to be adjusted, it is recommended that separate preparations of lamivudine and zidovudine are used in patients with severe hepatic impairment.

Haematological adverse reactions
Adjustment of zidovudine dosage may be necessary if the haemoglobin level falls below 9 g/dl or 5.59 mmol/litre or the neutrophil count falls below 1×10^9 /litre (see sections 4.3 and 4.4). As the dosage of Lamivudine/Zidovudine Tablets 150 mg/300 mg cannot be adjusted, separate preparations of zidovudine and lamivudine should be used.

Missed dose
If a dose is missed it should be taken as soon as it is noted. If the next dose is due in less than 6 hours, the forgotten dose should be skipped and the next regular dose taken when it is due. The patient should not take a double dose to make up for a missed dose.

4.3 Contraindications

Lamivudine/Zidovudine Tablets 150 mg/300 mg is contraindicated in patients with:
- Hypersensitivity to lamivudine, zidovudine or to any excipient in the formulation
- Abnormally low neutrophil count (< 0.75×10^9/litre) (see section 4.4),
- Abnormally low haemoglobin (< 7.5 g/dl or 4.65 mmol/litre) (see section 4.4).

4.4 Special warnings and precautions for use

[LMV-ZDV_150mg-300mg_SmPC_section 4-4 wo excipients]

4.5 Interaction with other medicinal products and other forms of interaction

As Lamivudine/Zidovudine Tablets 150 mg/300 mg contains lamivudine and zidovudine, any interactions that have been identified with these agents individually may occur.

Whereas lamivudine undergoes limited metabolism and is almost completely eliminated via the kidneys, zidovudine is primarily eliminated by hepatic conjugation, to form an inactive glucuronide metabolite.

Lamivudine and zidovudine are not significantly metabolised by cytochrome P450 enzymes (such as CYP3A4, CYP2C9 or CYP2D6) and do not inhibit or induce this enzyme system. Therefore, there is little potential for interactions with antiretroviral protease inhibitors, non-nucleosides and other medicinal products metabolised by major P450 enzymes.

The following list of interactions is not exhaustive, but is representative of the classes of medicinal products where caution should be exercised.

Drugs	**Interaction Geometric mean change (%) (Possible mechanism)**	**Recommendation concerning co-administration**
Antiretrovirals		
Emtricitabine/Lamivudine	Overlapping resistance and lack of additive antiretroviral effects.	Emtricitabine should not be co-administered with Lamivudine/Zidovudine Tablets 150 mg/300 mg.
Stavudine/Zidovudine	*In vitro* antagonism of anti-HIV activity between stavudine and zidovudine could result in	Stavudine should not be co-administered with Lamivudine/Zidovudine Tablets 150

	decreased efficacy of both drugs.	mg/300 mg.
Anti-infectives		
Clarithromycin/Zidovudine (500 mg twice daily/100 mg every 4 hours)	Zidovudine AUC ↓12%	Administration of Lamivudine/Zidovudine Tablets 150 mg/300 mg and clarithromycin should be separated by at least 2 hours.
Rifampicin/Zidovudine (600 mg once daily/200 mg three times daily)	Zidovudine AUC ↓48% (UGT induction)	Insufficient data to recommend dosage adjustment.
Trimethoprim + sulfamethoxazole/Lamivudine (160 mg/800 mg once daily for 5 days/300 mg single dose)	Lamivudine: AUC ↑40% Trimethoprim: AUC ↔ Sulfamethoxazole: AUC ↔ (Organic cation transporter inhibition)	No dosage adjustment of Lamivudine/Zidovudine Tablets 150 mg/300 mg is necessary, unless patient has renal impairment (section 4.2). When concomitant administration with trimethoprim + sulfamethaxazole is warranted, patients should be monitored clinically. High doses of trimethoprim + sulfamethoxazole for treating *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia and toxoplasmosis have not been studied and should be avoided.
Antifungal		
Fluconazole/Zidovudine (400 mg once daily/200 mg three times daily)	Zidovudine AUC ↑74% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8).
Antimalarial		
Atovaquone/Zidovudine (750 mg twice daily with food/200 mg three times daily)	Zidovudine AUC ↑33% Atovaquone AUC ↔	The clinical significance is not known.
Anticonvulsants		
Phenobarbital/Zidovudine	Interaction not studied. Potential to slightly decrease zidovudine plasma concentrations through UGT induction.	Insufficient data to recommend dosage adjustment.
Phenytoin/Zidovudine	Phenytoin AUC ↑↓	Monitor phenytoin concentration.
Valproic acid/Zidovudine (250 mg or 500 mg three times daily/100 mg three times daily)	Zidovudine AUC ↑80% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8).
Cytotoxics		
Cladribine/Lamivudine	Interaction not studied *In vitro* lamivudine inhibits the intracellular phosphorylation of cladribine leading to a potential risk of cladribine loss of efficacy in case of combination in the clinical setting. Some clinical findings also support a possible interaction between lamivudine and cladribine	Therefore the concomitant use of lamivudine with cladribine is not recommended (see section 4.4)
Opioids		
Methadone/Zidovudine (30–90 mg once daily/200 mg every 4 hours)	Zidovudine AUC ↑43% Methadone AUC ↔	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8). Methadone dosage adjustment may

		be required only occasionally.
Uricosuric		
Probenecid/Zidovudine(500 mg four times daily/2 mg/kg three times daily)	Zidovudine AUC ↑106% (UGT inhibition)	The clinical significance is not known. Monitor for signs of zidovudine toxicity (section 4.8).
Miscellaneous		
Sorbitol solution (3.2g, 10.2g, 13.4g) /Lamivudine	Single dose lamivudine oral solution 300mg Lamivudine: AUC ↓ 14%; 32%; 36% Cmax ↓ 28%; 52%: 55%	When possible, avoid chronic coadministration of Lamivudine/Zidovudine Tablets 150 mg/300 mg with medicinal products containing sorbitol or other osmotic acting poly-alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided
↑ = Increase ↔ = no significant change ↓ = decrease	AUC = area under the concentration versus time curve Cmax = maximum observed concentration	

Ribavirin can exacerbate anaemia when zidovudine is also part of the regimen used to treat HIV. Therefore, concomitant use of ribavirin with Lamivudine/Zidovudine Tablets 150 mg/300 mg is not recommended (see section 4.4), particularly in patients with a history of zidovudine-induced anaemia.
Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, trimethoprim + sulfamethoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) and zidovudine may increase the risk of adverse reactions. If concomitant therapy with Lamivudine/Zidovudine Tablets 150 mg/300 mg and any of these medicines is necessary then extra care should be taken to monitor renal function and haematological parameters and, if required, the dose of one or more agents should be reduced.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
No increased risk of birth defects has been reported for lamivudine or for zidovudine (www.apregistry.com), However, risks to the fetus cannot be ruled out.

The use in pregnant women of zidovudine alone, with subsequent treatment of the newborn infants, can reduce the rate of maternal-fetal transmission of HIV-infection. No such data are available for lamivudine.

Breast-feeding
Both lamivudine and zidovudine are present in breast milk at concentrations similar to those in the serum. Current recommendations on HIV and breast-feeding (e.g. those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility
Neither zidovudine nor lamivudine have impaired fertility in studies in male and female rats. There are no data on their effect on human female fertility.

In men, zidovudine has not been shown to affect sperm count, morphology or motility.

4.7 Effects on ability to drive and use machines

No studies are available on the effects of Lamivudine/Zidovudine Tablets 150 mg/300 mg on the ability to drive and use machines. Nevertheless, the clinical status of the patient and the adverse reaction profile of Lamivudine/Zidovudine Tablets 150 mg/300 mg should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

As Lamivudine/Zidovudine Tablets 150 mg/300 mg contains lamivudine and zidovudine, the type and severity of adverse reactions associated with each of the compounds may be expected. There is no evidence of added toxicity with concurrent administration of the two compounds.

The most frequently reported adverse reactions are headache and nausea. The most common serious adverse reactions include anaemia (which may require transfusions), neutropenia and leucopenia (see section 4.4).

Adverse events considered to be at least possibly related to treatment with zidovudine and lamivudine, are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (1/100–1/10), uncommon (1/1000–1/100), rare (1/10 000–1/1000) or very rare (≤ 1/10 000). In addition, adverse events identified during post-approval use of lamivudine, zidovudine, and lamivudine/zidovudine as a fixed-dose combination are listed but their frequency cannot be estimated (frequency category: 'unknown').

Blood and lymphatic systems disorders
Common: Anaemia, neutropenia, leucopenia *Uncommon*: Thrombocytopenia, pancytopenia
Rare: Pure red cell aplasia
Very rare: Aplastic anaemia

Metabolic and nutrition disorders
Rare: Lactic acidosis, anorexia
Unknown: Lipoatrophy, weight increase, hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia, (see section 4.4)

Psychiatric disorders
Rare: anxiety, depression

Nervous system disorders
Very common: Headache
Common: Dizziness, insomnia
Rare: Paraesthesia, somnolence, loss of mental acuity, convulsions

Cardiac disorders
Rare: Cardiomyopathy

Respiratory, thoracic and mediastinal disorders
Common: Cough, nasal symptoms
Uncommon: Dyspnoea

Gastrointestinal disorders
Very common: Nausea
Common: Vomiting, abdominal pain or cramps, diarrhoea
Uncommon: Flatulence
Rare: Pancreatitis, raised serum amylase, oral mucosa pigmentation, taste perversion, dyspepsia

Hepatobiliary disorders
Common: Elevated liver enzymes and bilirubin
Rare: Hepatitis, severe hepatomegaly with steatosis

Skin and subcutaneous tissue disorders
Common: Rash, hair loss
Uncommon: Pruritus
Rare: Nail and skin pigmentation, urticaria, sweating, angioedema

Musculoskeletal and connective tissue disorders
Common: Arthralgia, myalgia
Uncommon: Myopathy *Rare*: Rhabdomyolysis *Unknown*: osteonecrosis

Renal and urinary disorders
Rare: Urinary frequency

Reproductive system and breast disorders
Rare: Gynaecomastia

General disorders and administration site disorders:
Common: Malaise, fatigue, fever
Uncommon: Asthenia, generalised pain
Rare: Chest pain, influenza-like syndrome, chills
Unknown: Immune reconstitution syndrome (see section 4.4) See also sections 4.4 and 4.5

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

For reporting of adverse events and PV related queries please write to Email: ProductSafety@viatris.com

4.9 Overdose

There is limited experience of overdosage with lamivudine/zidovudine. No specific signs and symptoms have been identified following acute overdose with zidovudine or lamivudine apart from those listed as undesirable effects. No fatalities occurred and the patients recovered. If overdose occurs patients should be monitored for toxicity (see section 4.8), and standard supportive treatment given as necessary. Since elimination of lamivudine and the glucuronide metabolite of zidovudine are enhanced by haemodialysis, continuous haemodialysis could be used in the treatment of overdosage (but this has not been studied).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HIV infections, combinations, ATC Code J05AR01

Mechanism of action:
Lamivudine and zidovudine are nucleoside analogues that are active against HIV. Additionally, lamivudine has activity against hepatitis B virus (HBV). Both compounds are metabolised intracellularly to their active moieties, lamivudine 5'-triphosphate (TP) and zidovudine 5'-triphosphate respectively. Their main modes of action are as chain terminators of viral reverse transcription.

Lamivudine-TP and zidovudine-TP have selective inhibitory activity against HIV-1 and HIV-2 replication in vitro; lamivudine is also active against zidovudine-resistant clinical isolates of HIV. Lamivudine in combination with zidovudine exhibits synergistic anti-HIV activity against clinical isolates in cell culture.

Clinical efficacy:
In clinical trials, lamivudine and zidovudine in combination with a third antiretroviral agent reduce HIV-1 viral load and increases CD4 cell count. In a trial of zidovudine and lamivudine in combination with efavirenz, 68% of subjects achieved plasma HIV RNA < 50 copies/ml after 48 weeks, by intention-to-treat analysis. Lamivudine and zidovudine have been widely used as components of antiretroviral combination therapy with other antiretroviral agents.

Resistance:
In the great majority of cases when combination antiretroviral therapy comprising zidovudine and lamivudine fails virologically, the M184V mutation will be selected for at an early stage. M184V causes high-level resistance to lamivudine (> 300-fold reduced susceptibility). In vitro data suggest that continuation of lamivudine in antiretroviral regimen despite the development of M184V might provide residual antiretroviral activity (likely through impaired viral fitness). The clinical relevance of these findings is not established. Indeed, available clinical data are very limited and preclude any reliable conclusion in the field. Therefore, maintaining lamivudine therapy despite emergence of M184V mutation should be considered only when the activity of the best available NRTI backbone is significantly compromised.

On virological failure, resistance to zidovudine is developed along two separate, though not mutually exclusive, pathways. The first of these include M41L, L210W and T215F/Y. The second includes D67N, K70R and K219E/Q. Collectively these mutations are termed ‘thymidine analogue mutations’ (TAM). In viruses with M184V, two to three

TAMs are generally required for phenotypically detectable and clinically significant zidovudine resistance. M41L, L210W, and T215Y have a greater effect on zidovudine susceptibility and cross-resistance to other NRTIs than the other TAMs. Other important mutations selected for by zidovudine include T69 insertion mutations and the Q151M complex, where this mutation appears in combination with mutations at positions 75, 77, and 116. Both of these patterns confer high-level resistance to zidovudine and all other presently available NRTIs.

The likelihood of a gradual accumulation of mutations conferring resistance to the entire class of NRTI, upon virological failure with combination therapy including zidovudine and lamivudine, underscores the importance of early detection of virological failure. Delayed detection of virological failure may severely limit the options for second-line therapy.

The combination of lamivudine and zidovudine has not been specifically investigated in HIV patients co- infected with HBV.

5.2 Pharmacokinetic properties

Pharmacokinetics of Lamivudine and Zidovudine

	Lamivudine	**Zidovudine**
Absorption		
Oral bioavailability	80-85%	60-70%
Distribution		
Volume of distribution (mean)	1.3 L/kg	1.6 L/kg
Plasma proteinbindingin vitro	< 36%	34-38%
Metabolism		
	Only minor route (< 10%)	Glucuronidation Major metabolite: 5'-zidovudine-glucuronide
Active metabolite(s)	None	None
Elimination		
Elimination half life	5–7 hours 22 hours for intracellular lamivudine triphosphate	1.1 hours [IV] 7 hours [intracellular zidovudine triphosphate]
Mean systemic clearance (Cl/F)	0.32 L/hour/kg	0.34 L/hour/kg
% of dose excreted in urine	> 70% (Predominantly cleared unchanged)	> 50–80%
% of dose excreted in faeces	NA*	NA*
Pharmacokinetic linearity	Linear pharmacokinetics	NA*
Drug interactions *(in vitro*)		
Transporters	OCT (organic cationic transporters)	
Metabolising enzymes	-	UGT- Uridine 5'-diphospho-glucuronosyltransferase

NA* = Information not available

Pharmacokinetics in pregnancy
The pharmacokinetics of lamivudine and zidovudine during pregnancy were similar to that of non- pregnant women.

Pharmacokinetics in children
In children over the age of 5–6 months, the pharmacokinetic profile of zidovudine is similar to that in adults.
In general, lamivudine pharmacokinetics in paediatric patients are similar to adults

5.3 Preclinical safety data

Neither lamivudine nor zidovudine is mutagenic in bacterial tests, but like many nucleoside analogues they show activity in mammalian in vitro tests such as the mouse lymphoma assay. Lamivudine has not shown any genotoxic activity in in vivo studies at doses that produced plasma concentrations up to 40–50 times higher than clinical plasma levels. Zidovudine showed clastogenic effects in an oral repeated dose micronucleus test in mice.
A transplacental genotoxicity study in monkeys compared zidovudine alone with the combination of zidovudine and lamivudine at exposures equivalent to those in humans. That study demonstrated that fetuses exposed in utero to the combination sustained a higher level of nucleoside analogue-DNA incorporation into multiple fetal organs, and showed evidence of more telomere shortening than in those exposed to zidovudine alone. The clinical significance of these findings is unknown.
The carcinogenic potential of a combination of lamivudine and zidovudine has not been tested. In oral carcinogenicity studies in rats and mice, lamivudine did not show any carcinogenic potential. In oral carcinogenicity studies with zidovudine in mice and rats, late-appearing vaginal epithelial tumours were observed. The vaginal tumours were the result of long-term local exposure of the rodent vaginal epithelium to high concentrations of unmetabolised zidovudine in urine.
In addition, two transplacental carcinogenicity studies have been conducted in mice. In one study zidovudine an increase in the incidence of tumours in the lung, liver and female reproductive tract of offspring exposed to the highest dose level (420 mg/kg term body weight) were seen.
In a second study, mice were administered zidovudine at doses up to 40 mg/kg for 24 months. The second study thus provided no evidence that zidovudine acts as a transplacental carcinogen.
While the clinical relevance of these findings is unknown, these data suggest that a carcinogenic risk to humans is outweighed by the potential clinical benefit.
In reproductive toxicity studies lamivudine has demonstrated evidence of increasing early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man, but not in the rat even at very high systemic exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of fetal abnormalities was observed at lower doses.
In reproductive toxicity studies lamivudine has demonstrated evidence of increasing early embryonic deaths in the rabbit at relatively low systemic exposures, comparable to those achieved in man, but not in the rat even at very high systemic exposure. Zidovudine had a similar effect in both species, but only at very high systemic exposures. Lamivudine was not teratogenic in animal studies. At maternally toxic doses, zidovudine given to rats during organogenesis resulted in an increased incidence of malformations, but no evidence of fetal abnormalities was observed at lower doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Colloidal anhydrous silica, Sodium starch glycolate Magnesium stearate Hypromellose Titanium dioxide Propylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container Blister pack

HDPE bottle pack

HDPE bottle pack comprises white opaque HDPE bottle with screw cap. Seal made of aluminium foil is used in the

samples. Bottle of 60s.

6.6 Instructions for use and handling and disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Mylan Laboratories Limited, India
Email: ProductSafety@viatris.com

8. Mfd. by:

Mylan Laboratories Limited,
F-4 & F-12, Malegaon MIDC, Sinnar
Nashik - 422 113,
Maharashtra, India.

Mylan Laboratories Limited,
Plot No. H-12 & H-13
MIDC, Waluj Industrial Area,
Aurangabad. – 431136,
Maharashtra State, India.

Mylan Laboratories Limited,
Plot No. 11, 12 &13,
Indore Special Economic Zone,
Pharma Zone, Phase-II Sector-III,
Pithampur-454775, Dist. Dhar,
Madhya Pradesh, INDIA.

9. DATE OF REVISION OF THE TEXT

December 2019

10. References

The main reference source for this text is the European SPC for Combivir, available at: http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000190/WC500032326.pdf _ (accessed on May 21, 2018)

Further references relevant to sections of the SPC include:

Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach - second edition 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/

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Section 5.1

Clinical efficacy

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Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal/ .

Zambia Regn No.: 014/021
Zimbabwe Regn No.: 2008/7.13/4534
Botswana Regn No.: BOT 0801282
Rwanda Regn No.: Rwanda FDA-HMP-MA-0347
Namibia Regn No.: 10/20.2.8/0204
Namibia Scheduling Status: NS2

POM	**Schedule 2**	**PP**	**List - 1**

Mylan