OCCUPATIONAL EXPOSURE BAND SUMMARY

Chemical Name Amlodipine besylate

CAS Number(s) 111470-99-6

Pharmacological Class Calcium channel blocker

Chemical Class Dihydropyridinecarboxylic acids and derivatives

Hazards Identified	**YES**	**NO**	**UNKNOWN**
Genotoxic	☐	☒	☐
Toxic to reproduction or development	☒	☐	☐
Carcinogen	☐	☒	☐
Sensitizer	☐	☒	☐

Occupational Exposure Band (OEB) 10 μg/m^3 to 100 μg/m^3

The NIOSH Occupational Exposure Banding Process for Chemical Risk Management (NIOSH, 2019)

Applicability

This OEB applies only to amlodipine besylate.

Basis for the Occupational Exposure Band

Amlodipine besylate is a medication for reducing blood pressure with a daily oral dose of 5-10 mg.

- Amlodipine besylate has low oral toxicity (rat oral LD_{50} ≥393 mg/kg).
- In rats, repeated exposure to amlodipine besylate caused changes in the heart and adrenal glands with an oral 1-year NOAEL of 2 mg/kg/day.
- A severe eye irritant, amlodipine besylate is not a skin irritant or skin sensitizer and is not genotoxic or carcinogenic.
- Amlodipine besylate did not harm fertility or cause malformations but was harmful to development in rats at a dose of 7 mg/kg/day.
- An innovator-derived occupational exposure limit of 100 μg/m^3 is reported (Pfizer, 2018); the basis of this limit was not identified.

Per the NIOSH Occupational Exposure Banding Process, an oral repeat dose NOAEL >1 to ≤10 mg/kg/day corresponds to a NIOSH Band D (10 μg/m^3 to 100 μg/m^3). Additionally, the developmental toxicity was observed at exposures that correspond to a Band D.

Signs/Symptoms of Exposure

Nausea, lack of energy (lethargy) and dizziness are the most common symptoms of acute exposure to blood pressure medications of this class (calcium channel blockers). Symptoms typically develop within 2-3 hours of exposure and may persist for more than a day.

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OCCUPATIONAL EXPOSURE BAND DETERMINATION

Chemical Name	Amlodipine besylate
CAS Number(s)	111470-99-6
Pharmacological Class	Calcium channel blocker
Chemical Class	Dihydropyridinecarboxylic acids and derivatives

1. METHODS

An Occupational Exposure Band (OEB) is a qualitative assessment not intended to replace an Occupational Exposure Limit (OEL). Rather, an OEB is intended to inform risk management when insufficient information is available from which to derive an OEL (NIOSH, 2019).

The National Institute of Occupational Safety and Health (NIOSH) recently released a technical report describing an occupational exposure banding process (NIOSH, 2019). The methods used here are consistent with those described by NIOSH. Per the NIOSH rubric, the lowest exposure limit 0.01 mg/m^3 (10 μg/m^3), but within the pharmaceutical industry there is a need to identify exposure limits to <1 μg/m^3. To enable assessment of active pharmaceutical ingredients at limits <10 μg/m^3, the banding rubric described by Faber and colleagues (2014) is used as a supplement that defined by NIOSH.

1.2 Scope

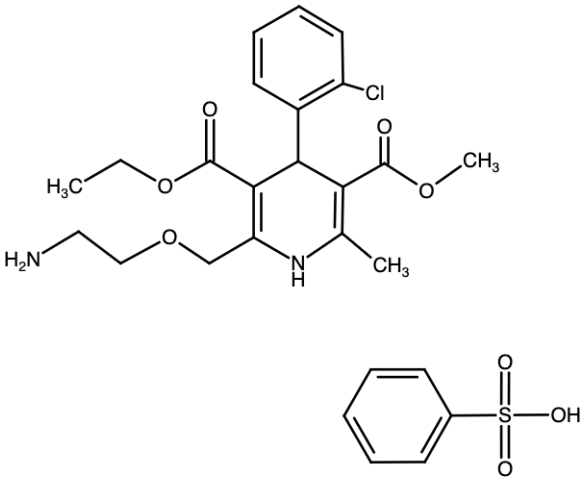
The pharmacokinetic and toxicologic properties of an active pharmaceutic ingredient can be greatly influenced by the salt form (Thackaberry, 2012). Specifically, different salt forms of amlodipine (e.g. maleate) are shown to contain chemical impurities not found in amlodipine besylate (Meredith, 2009). Because impurities that arise from different salt forms can exert biological activity or have different risks with respect to toxicity, this assessment is limited to amlodipine besylate (111470-99-6).

2. ASSESSMENT

2.1 Physicochemical Properties

The physicochemical properties of amlodipine besylate are summarized in Table 1.

Table 1. Physicochemical properties of amlodipine besylate

Common Name:	Amlodipine besylate
Systematic Name:	3,5-Pyridinedicarboxylic acid, 2-((2-aminoethoxy)methyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl-5-methyl ester, monobenzenesulfonate
CAS Number:	111470-99-6
Molecular Formula:	$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$
Structural Formula:	
Molecular Weight:	567.0559
Physical State/Appearance:	White to off-white powder (Mylan, 2018)
Solubility (water):	Slightly soluble (Mylan, 2018)

Reference: ChemIDPlus except as noted.

2.2 Clinical Summary

2.2.1 Therapeutic Indication and Dose

Amlodipine besylate is approved for the treatment of high blood pressure and coronary artery disease including angina (DrugBank, 2019). The recommended starting dose is 5 mg amlodipine besylate by mouth once daily with a maximum dose of 10 mg once daily (DailyMed, 2019).

2.2.2 Pharmacology

A calcium ion antagonist that inhibits the influx of calcium ions into vascular smooth muscle and cardiac muscle, amlodipine is a peripheral arterial vasodilator that reduces peripheral vascular resistance and thereby reduces blood pressure (DailyMed, 2019). The exact mechanism by which amlodipine relieves angina is not entirely understood.

2.2.3 Pharmacokinetics

Amlodipine besylate is 64-90% bioavailable with peak plasma concentrations 6 to 12 hours after oral administration (DailyMed, 2019). The therapeutic half-life of amlodipine besylate is approximately 30-50 hours with metabolites excreted in the urine.

2.2.4 Effects in Humans

Nausea, lack of energy (lethargy) and dizziness are the symptoms of mild calcium channel blocker toxicity (TOXINZ, 2019). Symptoms typically develop within 2-3 hours after exposure and may persist for more than a day.

Moderate calcium channel blocker toxicity manifests as vomiting, drowsiness, hypotension, sinus bradycardia, isolated junctional rhythm and ileus (obstruction of the intestine). Fatalities have occurred in adults following ingestion of 50 to 150 mg amlodipine.

2.3 Nonclinical Summary

2.3.1 Acute Toxicity

The acute toxicity of amlodipine besylate is summarized in Table 2.

Table 2. Acute oral toxicity of amlodipine besylate

Route	Species		Endpoint	Value	Reference
Oral	Mouse		LD_{50}	37 mg/kg	(RTECS, 2010)
	Rat	Male	LD_{50}	393 mg/kg	(Pfizer, 2017)
		Female	LD_{50}	686 mg/kg	

2.3.2 Repeat-Dose Toxicity

A 1-month repeat dose toxicity study in rats evaluated oral doses of 4, 16, 32, and 64 mg/kg/day amlodipine besylate (Pfizer, 2017). Mortality was observed at 32 and 64 mg/kg/day. Increased heart weights, increased urinary volume, and increased blood urea nitrogen (BUN) were observed at 16 mg/kg/day and higher.

A 6-month repeat dose toxicity study in rats evaluated oral doses of 2.5, 5, and 10 mg/kg/day amlodipine besylate (Pfizer, 2017). Increased urinary volume, increased electrolyte (sodium, potassium, chloride) excretion, and increased heart weights were observed at all doses. Histopathological changes in the adrenal gland (thickening of the zona glomerulosa) were observed at 5 and 10 mg/kg/day.

A 6-month repeat dose toxicity study in dogs evaluated oral doses of 0.25, 0.5, and 1 mg/kg/day amlodipine besylate (Pfizer, 2017). Increased urinary volume with increased excretion of electrolytes, and reduction in blood pressure with increases in

heart rate were observed at all doses. Relative heart weights were increased at 1 mg/kg/day.

A 12-month repeat dose toxicity study in rats evaluated oral doses of 1.4, 7, and 18 mg/kg/day amlodipine besylate (Pfizer, 2017). Mortality was observed at 18 mg/kg/day. Increased relative heart weight and enlargement of the zona glomerulosa of adrenals were observed at 7 and 18 mg/kg/day.

A 12-month repeat dose toxicity study in dogs evaluated oral doses of 0.125, 0.25, and 0.5 mg/kg/day amlodipine besylate (Pfizer, 2017). A reduction in blood pressure with increased heart rate and increased urinary volume with excretion of electrolytes was observed at 0.5 mg/kg/day.

The LOEL/NOAEL values reported by the innovator are summarized in Table 3.

Table 3. LOEL/NOAEL values for amlodipine besylate (Pfizer, 2017)

Route	Species	Duration	Endpoint	Value
Oral	Rat	1 month	LOEL	3.5 mg/kg/day
		3 months	NOAEL	3 mg/kg/day
		1 year	NOAEL	2 mg/kg/day

2.3.3 Reproductive/Developmental Toxicity

Amlodipine besylate is not toxic to reproduction (fertility) in rats or teratogenic in rats or rabbits (Pfizer, 2017). There was some evidence of developmental toxicity (decreased number of viable pups at birth and day 4 post-partum) at 7 mg/kg/day (Pfizer, 2017). The next lowest dose in this study (the putative NOAEL) was 2.8 mg/kg/day. A study in the peer-reviewed literature reports a mouse NOAEL of 0.2 mg/kg/day for developmental toxicity (Orisakwe et al., 2000).

The innovator reports a rat NOAEL of 4 mg/kg/day for fetotoxicity/fetal mortality (Pfizer, 2009).

2.3.4 Genotoxicity

Amlodipine besylate was not genotoxic in a standard battery of *in vitro* and *in vivo* assays (Pfizer, 2017).

2.3.5 Carcinogenicity

Amlodipine besylate was not carcinogenic in mice or rats in 2-year bioassays (Pfizer, 2017).

2.3.6 Irritation/Sensitization

Amlodipine besylate is a severe eye irritant but not irritating to the skin and not a skin sensitizer (Pfizer, 2009).

2.3.7 Other Toxicological Information

An innovator-derived occupational exposure limit of 100 μg/m^3 is reported (Pfizer, 2018; the basis of this limit was not identified. This document is not intended to confirm or refute the innovator-derived limit. In most instances, proprietary data (not available for this assessment) inform such innovator-derived limits.

3. OCCUPATIONAL EXPOSURE BAND DERIVATION

Per the NIOSH banding process (NIOSH, 2019), the NOAEL values for the repeat dose toxicity studies are indicative of an occupational exposure band (OEB) of 10 to 100 μg/m^3. Additionally, while amlodipine besylate is not toxic to reproduction and is not teratogenic, data in mice and rats indicate potential developmental toxicity. The threshold for these effects was sufficiently low as to indicate an OEB of 10 to 100 μg/m^3.

The preponderance of information supports an OEB of 10 μg/m^3 to 100 μg/m^3 for amlodipine besylate.

4. REFERENCES

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