

Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide Tablets

Piramal Pharma Limited

Chemwatch: 7985-99
Version No: 2.1
Safety Data Sheet

Chemwatch Hazard Alert Code: 2

Initial Date: 31/10/2025
Revision Date: 31/10/2025
Print Date: 03/11/2025
L.GHS.IND.EN.RISK

SECTION 1 Identification of the substance / mixture and of the company / undertaking

Product Identifier

Product name	Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide Tablets
Chemical Name	Not Applicable
Synonyms	Not Available
Chemical formula	Not Applicable
Other means of identification	Not Available

Relevant identified uses of the substance or mixture and uses advised against

Relevant identified uses	Medicine/tablets. Use according to manufacturer's directions.
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Details of the manufacturer or importer of the safety data sheet

Registered company name	Piramal Pharma Limited
Address	67-70 Sector II, Industrial Area Pithampur Madhya Pradesh 454775 India
Telephone	07292-428431
Fax	Not Available
Website	https://www.piramalpharma.com/
Email	uday.girase@piramal.com

Emergency telephone number

Association / Organisation	Uday Girase	CHEMWATCH EMERGENCY RESPONSE (24/7)
Emergency telephone number(s)	07292-428403	+918000403230 (ID#: 7985-99)
Other emergency telephone number(s)	Not Available	+61 3 9573 3188

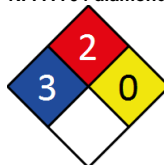
SECTION 2 Hazards identification

Classification of the substance or mixture

Chemwatch Hazard Ratings

	Min	Max
Flammability	1	2
Toxicity	2	3
Body Contact	2	3
Reactivity	1	2
Chronic	2	3

NFPA 704 diamond



0 = Minimum
1 = Low
2 = Moderate
3 = High
4 = Extreme

Note: The hazard category numbers found in GHS classification in section 2 of this SDSs are NOT to be used to fill in the NFPA 704 diamond. Blue = Health Red = Fire Yellow = Reactivity White = Special (Oxidizer or water reactive substances)

Classification	Acute Toxicity (Oral) Category 4, Skin Corrosion/Irritation Category 3, Sensitisation (Skin) Category 1, Serious Eye Damage/Eye Irritation Category 1, Sensitisation (Respiratory) Category 1, Specific Target Organ Toxicity - Single Exposure (Respiratory Tract Irritation) Category 3, Germ Cell Mutagenicity Category 2, Reproductive Toxicity Category 2, Specific Target Organ Toxicity - Repeated Exposure Category 2, Hazardous to the Aquatic Environment Long-Term Hazard Category 3 <i>*LIMITED EVIDENCE</i>
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Label elements

Hazard pictogram(s)	
Signal word	Danger

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Hazard statement(s)

H302	Harmful if swallowed.
H316	Causes mild skin irritation.
H317	May cause an allergic skin reaction.
H318	Causes serious eye damage.
H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H335	May cause respiratory irritation.
H341	Suspected of causing genetic defects.
H361	Suspected of damaging fertility or the unborn child.
H373	May cause damage to organs through prolonged or repeated exposure.
H412	Harmful to aquatic life with long lasting effects.

*LIMITED EVIDENCE

Precautionary statement(s) Prevention

P260	Do not breathe dust/fume.
P271	Use only outdoors or in a well-ventilated area.
P280	Wear protective gloves, protective clothing, eye protection and face protection.
P284	[In case of inadequate ventilation] wear respiratory protection.
P264	Wash all exposed external body areas thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P273	Avoid release to the environment.
P202	Do not handle until all safety precautions have been read and understood.
P272	Contaminated work clothing should not be allowed out of the workplace.

Precautionary statement(s) Response

P304+P340	IF INHALED: Remove person to fresh air and keep comfortable for breathing.
P305+P351+P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P308+P313	IF exposed or concerned: Get medical advice/ attention.
P310	Immediately call a POISON CENTER/doctor/physician/first aider.
P342+P311	If experiencing respiratory symptoms: Call a POISON CENTER/doctor/physician/first aider.
P302+P352	IF ON SKIN: Wash with plenty of water and soap.
P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
P362+P364	Take off contaminated clothing and wash it before reuse.
P301+P312	IF SWALLOWED: Call a POISON CENTER/doctor/physician/first aider if you feel unwell.
P330	Rinse mouth.

Precautionary statement(s) Storage

P405	Store locked up.
P403+P233	Store in a well-ventilated place. Keep container tightly closed.

Precautionary statement(s) Disposal

P501	Dispose of contents/container to authorised hazardous or special waste collection point in accordance with any local regulation.
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No further product hazard information.

SECTION 3 Composition / information on ingredients

Substances

See section below for composition of Mixtures

Mixtures

CAS No	%[weight]	Name
9004-34-6	30-60	<u>cellulose</u>
9005-25-8	10-30	<u>starch</u>
144689-63-4	10-30	<u>olmesartan medoxomil</u>
58-93-5	1-10	<u>hydrochlorothiazide</u>
111470-99-6	1-10	<u>amlodipine besylate</u>
14807-96-6	<1	<u>talc</u>
Not Available	balance	Ingredients determined not to be hazardous

SECTION 4 First aid measures

Description of first aid measures

Eye Contact	If this product comes in contact with the eyes: ▶ Immediately hold eyelids apart and flush the eye continuously with running water.
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	<ul style="list-style-type: none"> ▶ Ensure complete irrigation of the eye by keeping eyelids apart and away from eye and moving the eyelids by occasionally lifting the upper and lower lids. ▶ Continue flushing until advised to stop by the Poisons Information Centre or a doctor, or for at least 15 minutes. ▶ Transport to hospital or doctor without delay. ▶ Removal of contact lenses after an eye injury should only be undertaken by skilled personnel.
Skin Contact	<p>If skin contact occurs:</p> <ul style="list-style-type: none"> ▶ Immediately remove all contaminated clothing, including footwear. ▶ Flush skin and hair with running water (and soap if available). ▶ Seek medical attention in event of irritation.
Inhalation	<ul style="list-style-type: none"> ▶ If fumes or combustion products are inhaled remove from contaminated area. ▶ Lay patient down. Keep warm and rested. ▶ Prostheses such as false teeth, which may block airway, should be removed, where possible, prior to initiating first aid procedures. ▶ Apply artificial respiration if not breathing, preferably with a demand valve resuscitator, bag-valve mask device, or pocket mask as trained. Perform CPR if necessary. ▶ Transport to hospital, or doctor, without delay.
Ingestion	<ul style="list-style-type: none"> ▶ IF SWALLOWED, REFER FOR MEDICAL ATTENTION, WHERE POSSIBLE, WITHOUT DELAY. ▶ For advice, contact a Poisons Information Centre or a doctor. ▶ Urgent hospital treatment is likely to be needed. ▶ In the mean time, qualified first-aid personnel should treat the patient following observation and employing supportive measures as indicated by the patient's condition. ▶ If the services of a medical officer or medical doctor are readily available, the patient should be placed in his/her care and a copy of the SDS should be provided. Further action will be the responsibility of the medical specialist. ▶ If medical attention is not available on the worksite or surroundings send the patient to a hospital together with a copy of the SDS. <p>Where medical attention is not immediately available or where the patient is more than 15 minutes from a hospital or unless instructed otherwise:</p> <ul style="list-style-type: none"> ▶ INDUCE vomiting with fingers down the back of the throat, ONLY IF CONSCIOUS. Lean patient forward or place on left side (head-down position, if possible) to maintain open airway and prevent aspiration. <p>NOTE: Wear a protective glove when inducing vomiting by mechanical means.</p>

Indication of any immediate medical attention and special treatment needed

Treat symptomatically.

As in all cases of suspected poisoning, follow the ABCDEs of emergency medicine (airway, breathing, circulation, disability, exposure), then the ABCDEs of toxicology (antidotes, basics, change absorption, change distribution, change elimination).

For poisons (where specific treatment regime is absent):

BASIC TREATMENT

- ▶ Establish a patent airway with suction where necessary.
- ▶ Watch for signs of respiratory insufficiency and assist ventilation as necessary.
- ▶ Administer oxygen by non-rebreather mask at 10 to 15 L/min.
- ▶ Monitor and treat, where necessary, for pulmonary oedema.
- ▶ Monitor and treat, where necessary, for shock.
- ▶ Anticipate seizures.
- ▶ **DO NOT** use emetics. Where ingestion is suspected rinse mouth and give up to 200 ml water (5 ml/kg recommended) for dilution where patient is able to swallow, has a strong gag reflex and does not drool.

ADVANCED TREATMENT

- ▶ Consider orotracheal or nasotracheal intubation for airway control in unconscious patient or where respiratory arrest has occurred.
- ▶ Positive-pressure ventilation using a bag-valve mask might be of use.
- ▶ Monitor and treat, where necessary, for arrhythmias.
- ▶ Start an IV D5W TKO. If signs of hypovolaemia are present use lactated Ringers solution. Fluid overload might create complications.
- ▶ Drug therapy should be considered for pulmonary oedema.
- ▶ Hypotension with signs of hypovolaemia requires the cautious administration of fluids. Fluid overload might create complications.
- ▶ Treat seizures with diazepam.
- ▶ Proparacaine hydrochloride should be used to assist eye irrigation.

BRONSTEIN, A.C. and CURRANCE, P.L.

EMERGENCY CARE FOR HAZARDOUS MATERIALS EXPOSURE: 2nd Ed. 1994

SECTION 5 Firefighting measures

Extinguishing media

- ▶ There is no restriction on the type of extinguisher which may be used.
- ▶ Use extinguishing media suitable for surrounding area.

Special hazards arising from the substrate or mixture

- | | |
|-----------------------------|--|
| Fire Incompatibility | ▶ Avoid contamination with oxidising agents i.e. nitrates, oxidising acids, chlorine bleaches, pool chlorine etc. as ignition may result |
|-----------------------------|--|

Advice for firefighters

Fire Fighting	<ul style="list-style-type: none"> ▶ Alert Fire Brigade and tell them location and nature of hazard. ▶ Wear breathing apparatus plus protective gloves in the event of a fire. ▶ Prevent, by any means available, spillage from entering drains or water courses. ▶ Use fire fighting procedures suitable for surrounding area. ▶ DO NOT approach containers suspected to be hot. ▶ Cool fire exposed containers with water spray from a protected location. ▶ If safe to do so, remove containers from path of fire. ▶ Equipment should be thoroughly decontaminated after use.
Fire/Explosion Hazard	<ul style="list-style-type: none"> ▶ Combustible solid which burns but propagates flame with difficulty; it is estimated that most organic dusts are combustible (circa 70%) - according to the circumstances under which the combustion process occurs, such materials may cause fires and / or dust explosions. ▶ Organic powders when finely divided over a range of concentrations regardless of particulate size or shape and suspended in air or some other oxidizing medium may form explosive dust-air mixtures and result in a fire or dust explosion (including secondary explosions). ▶ Avoid generating dust, particularly clouds of dust in a confined or unventilated space as dusts may form an explosive mixture with air, and any source of ignition, i.e. flame or spark, will cause fire or explosion. Dust clouds generated by the fine grinding of the solid are a

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particular hazard; accumulations of fine dust (420 micron or less) may burn rapidly and fiercely if ignited - particles exceeding this limit will generally not form flammable dust clouds; once initiated, however, larger particles up to 1400 microns diameter will contribute to the propagation of an explosion.

- ▶ In the same way as gases and vapours, dusts in the form of a cloud are only ignitable over a range of concentrations; in principle, the concepts of lower explosive limit (LEL) and upper explosive limit (UEL) are applicable to dust clouds but only the LEL is of practical use; - this is because of the inherent difficulty of achieving homogeneous dust clouds at high temperatures (for dusts the LEL is often called the "Minimum Explosible Concentration", MEC).
- ▶ When processed with flammable liquids/vapors/mists, ignitable (hybrid) mixtures may be formed with combustible dusts. Ignitable mixtures will increase the rate of explosion pressure rise and the Minimum Ignition Energy (the minimum amount of energy required to ignite dust clouds - MIE) will be lower than the pure dust in air mixture. The Lower Explosive Limit (LEL) of the vapour/dust mixture will be lower than the individual LELs for the vapors/mists or dusts.
- ▶ A dust explosion may release of large quantities of gaseous products; this in turn creates a subsequent pressure rise of explosive force capable of damaging plant and buildings and injuring people.
- ▶ Usually the initial or primary explosion takes place in a confined space such as plant or machinery, and can be of sufficient force to damage or rupture the plant. If the shock wave from the primary explosion enters the surrounding area, it will disturb any settled dust layers, forming a second dust cloud, and often initiate a much larger secondary explosion. All large scale explosions have resulted from chain reactions of this type.
- ▶ Dry dust can be charged electrostatically by turbulence, pneumatic transport, pouring, in exhaust ducts and during transport.
- ▶ Build-up of electrostatic charge may be prevented by bonding and grounding.
- ▶ Powder handling equipment such as dust collectors, dryers and mills may require additional protection measures such as explosion venting.
- ▶ All movable parts coming in contact with this material should have a speed of less than 1-meter/sec.
- ▶ A sudden release of statically charged materials from storage or process equipment, particularly at elevated temperatures and/ or pressure, may result in ignition especially in the absence of an apparent ignition source.
- ▶ One important effect of the particulate nature of powders is that the surface area and surface structure (and often moisture content) can vary widely from sample to sample, depending of how the powder was manufactured and handled; this means that it is virtually impossible to use flammability data published in the literature for dusts (in contrast to that published for gases and vapours).
- ▶ Autoignition temperatures are often quoted for dust clouds (minimum ignition temperature (MIT)) and dust layers (layer ignition temperature (LIT)); LIT generally falls as the thickness of the layer increases.

Combustion products include:

carbon monoxide (CO)
carbon dioxide (CO₂)
hydrogen chloride
phosgene
nitrogen oxides (NO_x)
sulfur oxides (SO_x)
silicon dioxide (SiO₂)
other pyrolysis products typical of burning organic material.
May emit poisonous fumes.
May emit corrosive fumes.

SECTION 6 Accidental release measures

Personal precautions, protective equipment and emergency procedures

See section 8

Environmental precautions

See section 12

Methods and material for containment and cleaning up

Minor Spills	<ul style="list-style-type: none"> ▶ Clean up waste regularly and abnormal spills immediately. ▶ Avoid breathing dust and contact with skin and eyes. ▶ Wear protective clothing, gloves, safety glasses and dust respirator. ▶ Use dry clean up procedures and avoid generating dust. ▶ Vacuum up or sweep up. NOTE: Vacuum cleaner must be fitted with an exhaust micro filter (H-Class HEPA type) (consider explosion-proof machines designed to be grounded during storage and use). H-Class HEPA filtered industrial vacuum cleaners should NOT be used on wet materials or surfaces. ▶ Dampen with water to prevent dusting before sweeping. ▶ Place in suitable containers for disposal.
Major Spills	<ul style="list-style-type: none"> ▶ Clear area of personnel and move upwind. ▶ Alert Fire Brigade and tell them location and nature of hazard. ▶ Wear full body protective clothing with breathing apparatus. ▶ Prevent, by all means available, spillage from entering drains or water courses. ▶ Consider evacuation (or protect in place). ▶ No smoking, naked lights or ignition sources. ▶ Increase ventilation. ▶ Stop leak if safe to do so. ▶ Water spray or fog may be used to disperse / absorb vapour. ▶ Contain or absorb spill with sand, earth or vermiculite. ▶ Collect recoverable product into labelled containers for recycling. ▶ Collect solid residues and seal in labelled drums for disposal. ▶ Wash area and prevent runoff into drains. ▶ After clean up operations, decontaminate and launder all protective clothing and equipment before storing and re-using. ▶ If contamination of drains or waterways occurs, advise emergency services.

Personal Protective Equipment advice is contained in Section 8 of the SDS.

SECTION 7 Handling and storage

Precautions for safe handling

Safe handling	<p>In general personnel handling this material and all conducting equipment should be electrically earthed or grounded. Consideration should be given to avoiding the use of insulating plastics.</p> <p>Bulk bags (FIBC) used to contain this material should be Type C or Type D. Type C bags must be electrically grounded before powder is charged to or discharged from the bag.</p> <p>Bag filters used to scavenge dust from material handling processes should be conductive and electrically grounded during use. If metal or fibre drums are used to contain this product, make certain that the metal parts are bonded to the filling equipment and grounded. This material can become readily charged in most/ many operations.</p> <ul style="list-style-type: none"> ▶ Avoid all personal contact, including inhalation.
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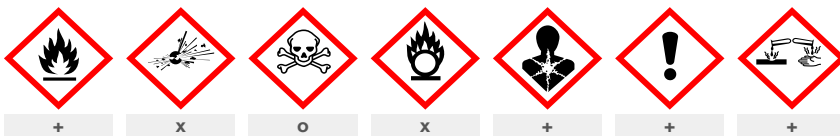
- ▶ Wear protective clothing when risk of exposure occurs.
 - ▶ Use in a well-ventilated area.
 - ▶ Prevent concentration in hollows and sumps.
 - ▶ **DO NOT enter confined spaces until atmosphere has been checked.**
 - ▶ **DO NOT allow material to contact humans, exposed food or food utensils.**
 - ▶ Avoid contact with incompatible materials.
 - ▶ **When handling, DO NOT eat, drink or smoke.**
 - ▶ Keep containers securely sealed when not in use.
 - ▶ Avoid physical damage to containers.
 - ▶ Always wash hands with soap and water after handling.
 - ▶ Work clothes should be laundered separately. Launder contaminated clothing before re-use.
 - ▶ Use good occupational work practice.
 - ▶ Observe manufacturer's storage and handling recommendations contained within this SDS.
 - ▶ Atmosphere should be regularly checked against established exposure standards to ensure safe working conditions are maintained.
 - ▶ Organic powders when finely divided over a range of concentrations regardless of particulate size or shape and suspended in air or some other oxidizing medium may form explosive dust-air mixtures and result in a fire or dust explosion (including secondary explosions)
 - ▶ Minimise airborne dust and eliminate all ignition sources. Keep away from heat, hot surfaces, sparks, and flame.
 - ▶ Establish good housekeeping practices.
 - ▶ Remove dust accumulations on a regular basis by vacuuming or gentle sweeping to avoid creating dust clouds.
 - ▶ Use continuous suction at points of dust generation to capture and minimise the accumulation of dusts. Particular attention should be given to overhead and hidden horizontal surfaces to minimise the probability of a "secondary" explosion. According to NFPA Standard 654, dust layers 1/32 in.(0.8 mm) thick can be sufficient to warrant immediate cleaning of the area.
 - ▶ Do not use air hoses for cleaning.
 - ▶ Minimise dry sweeping to avoid generation of dust clouds. Vacuum dust-accumulating surfaces and remove to a chemical disposal area. Vacuums with explosion-proof motors should be used.
 - ▶ Control sources of static electricity. Dusts or their packages may accumulate static charges, and static discharge can be a source of ignition.
 - ▶ Solids handling systems must be designed in accordance with applicable standards (e.g. NFPA including 654 and 77) and other national guidance.
 - ▶ Do not empty directly into flammable solvents or in the presence of flammable vapors.
 - ▶ The operator, the packaging container and all equipment must be grounded with electrical bonding and grounding systems. Plastic bags and plastics cannot be grounded, and antistatic bags do not completely protect against development of static charges.
- Empty containers may contain residual dust which has the potential to accumulate following settling. Such dusts may explode in the presence of an appropriate ignition source.
- ▶ **Do NOT cut, drill, grind or weld such containers.**
 - ▶ In addition ensure such activity is not performed near full, partially empty or empty containers without appropriate workplace safety authorisation or permit.

Other information

- ▶ Store in original containers.
 - ▶ Keep containers securely sealed.
 - ▶ Store in a cool, dry area protected from environmental extremes.
 - ▶ Store away from incompatible materials and foodstuff containers.
 - ▶ Protect containers against physical damage and check regularly for leaks.
 - ▶ Observe manufacturer's storage and handling recommendations contained within this SDS.
- For major quantities:
- ▶ Consider storage in bunded areas - ensure storage areas are isolated from sources of community water (including stormwater, ground water, lakes and streams).
 - ▶ Ensure that accidental discharge to air or water is the subject of a contingency disaster management plan; this may require consultation with local authorities.

Conditions for safe storage, including any incompatibilities

Suitable container	<ul style="list-style-type: none"> ▶ Glass container is suitable for laboratory quantities ▶ Polyethylene or polypropylene container. ▶ Check all containers are clearly labelled and free from leaks.
Storage incompatibility	<ul style="list-style-type: none"> ▶ Avoid strong acids, bases. ▶ Avoid reaction with oxidising agents



X — Must not be stored together
O — May be stored together with specific preventions
+ — May be stored together

Note: Depending on other risk factors, compatibility assessment based on the table above may not be relevant to storage situations, particularly where large volumes of dangerous goods are stored and handled. Reference should be made to the Safety Data Sheets for each substance or article and risks assessed accordingly.

SECTION 8 Exposure controls / personal protection

Control parameters

Occupational Exposure Limits (OEL)

INGREDIENT DATA


Not Available

Ingredient	Original IDLH	Revised IDLH
cellulose	Not Available	Not Available
starch	Not Available	Not Available
olmesartan medoxomil	Not Available	Not Available
hydrochlorothiazide	Not Available	Not Available
amlodipine besylate	Not Available	Not Available
talc	1,000 mg/m3	Not Available

MATERIAL DATA

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Exposure controls

<p>Appropriate engineering controls</p>	<p>Engineering controls are used to remove a hazard or place a barrier between the worker and the hazard. Well-designed engineering controls can be highly effective in protecting workers and will typically be independent of worker interactions to provide this high level of protection. The basic types of engineering controls are: Process controls which involve changing the way a job activity or process is done to reduce the risk. Enclosure and/or isolation of emission source which keeps a selected hazard "physically" away from the worker and ventilation that strategically "adds" and "removes" air in the work environment. Ventilation can remove or dilute an air contaminant if designed properly. The design of a ventilation system must match the particular process and chemical or contaminant in use. Employers may need to use multiple types of controls to prevent employee overexposure.</p> <ul style="list-style-type: none"> ▶ Employees exposed to confirmed human carcinogens should be authorized to do so by the employer, and work in a regulated area. ▶ Work should be undertaken in an isolated system such as a "glove-box" . Employees should wash their hands and arms upon completion of the assigned task and before engaging in other activities not associated with the isolated system. ▶ Within regulated areas, the carcinogen should be stored in sealed containers, or enclosed in a closed system, including piping systems, with any sample ports or openings closed while the carcinogens are contained within. ▶ Open-vessel systems are prohibited. ▶ Each operation should be provided with continuous local exhaust ventilation so that air movement is always from ordinary work areas to the operation. ▶ Exhaust air should not be discharged to regulated areas, non-regulated areas or the external environment unless decontaminated. Clean make-up air should be introduced in sufficient volume to maintain correct operation of the local exhaust system. ▶ For maintenance and decontamination activities, authorized employees entering the area should be provided with and required to wear clean, impervious garments, including gloves, boots and continuous-air supplied hood. Prior to removing protective garments the employee should undergo decontamination and be required to shower upon removal of the garments and hood. ▶ Except for outdoor systems, regulated areas should be maintained under negative pressure (with respect to non-regulated areas). ▶ Local exhaust ventilation requires make-up air be supplied in equal volumes to replaced air. ▶ Laboratory hoods must be designed and maintained so as to draw air inward at an average linear face velocity of 0.76 m/sec with a minimum of 0.64 m/sec. Design and construction of the fume hood requires that insertion of any portion of the employees body, other than hands and arms, be disallowed.
<p>Individual protection measures, such as personal protective equipment</p>	
<p>Eye and face protection</p>	<p>When handling very small quantities of the material eye protection may not be required. For laboratory, larger scale or bulk handling or where regular exposure in an occupational setting occurs:</p> <ul style="list-style-type: none"> ▶ Chemical goggles. [AS/NZS 1337.1, EN166 or national equivalent] ▶ Face shield. Full face shield may be required for supplementary but never for primary protection of eyes. ▶ Contact lenses may pose a special hazard; soft contact lenses may absorb and concentrate irritants. A written policy document, describing the wearing of lenses or restrictions on use, should be created for each workplace or task. This should include a review of lens absorption and adsorption for the class of chemicals in use and an account of injury experience. Medical and first-aid personnel should be trained in their removal and suitable equipment should be readily available. In the event of chemical exposure, begin eye irrigation immediately and remove contact lens as soon as practicable. Lens should be removed at the first signs of eye redness or irritation - lens should be removed in a clean environment only after workers have washed hands thoroughly. [CDC NIOSH Current Intelligence Bulletin 59].
<p>Skin protection</p>	<p>See Hand protection below</p>
<p>Hands/feet protection</p>	<p>NOTE:</p> <ul style="list-style-type: none"> ▶ The material may produce skin sensitisation in predisposed individuals. Care must be taken, when removing gloves and other protective equipment, to avoid all possible skin contact. ▶ Contaminated leather items, such as shoes, belts and watch-bands should be removed and destroyed. <p>The selection of suitable gloves does not only depend on the material, but also on further marks of quality which vary from manufacturer to manufacturer. Where the chemical is a preparation of several substances, the resistance of the glove material can not be calculated in advance and has therefore to be checked prior to the application. The exact break through time for substances has to be obtained from the manufacturer of the protective gloves and has to be observed when making a final choice. Personal hygiene is a key element of effective hand care. Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturiser is recommended. Suitability and durability of glove type is dependent on usage. Important factors in the selection of gloves include:</p> <ul style="list-style-type: none"> - frequency and duration of contact, - chemical resistance of glove material, - glove thickness and - dexterity <p>Select gloves tested to a relevant standard (e.g. Europe EN 374, US F739, AS/NZS 2161.1 or national equivalent).</p> <ul style="list-style-type: none"> - When prolonged or frequently repeated contact may occur, a glove with a protection class of 5 or higher (breakthrough time greater than 240 minutes according to EN 374, AS/NZS 2161.10.1 or national equivalent) is recommended. - When only brief contact is expected, a glove with a protection class of 3 or higher (breakthrough time greater than 60 minutes according to EN 374, AS/NZS 2161.10.1 or national equivalent) is recommended. - Some glove polymer types are less affected by movement and this should be taken into account when considering gloves for long-term use. - Contaminated gloves should be replaced. <p>As defined in ASTM F-739-96 in any application, gloves are rated as:</p> <ul style="list-style-type: none"> - Excellent when breakthrough time > 480 min - Good when breakthrough time > 20 min - Fair when breakthrough time < 20 min - Poor when glove material degrades <p>For general applications, gloves with a thickness typically greater than 0.35 mm, are recommended. It should be emphasised that glove thickness is not necessarily a good predictor of glove resistance to a specific chemical, as the permeation efficiency of the glove will be dependent on the exact composition of the glove material. Therefore, glove selection should also be based on consideration of the task requirements and knowledge of breakthrough times. Glove thickness may also vary depending on the glove manufacturer, the glove type and the glove model. Therefore, the manufacturers technical data should always be taken into account to ensure selection of the most appropriate glove for the task. Note: Depending on the activity being conducted, gloves of varying thickness may be required for specific tasks. For example:</p> <ul style="list-style-type: none"> - Thinner gloves (down to 0.1 mm or less) may be required where a high degree of manual dexterity is needed. However, these gloves are only likely to give short duration protection and would normally be just for single use applications, then disposed of. - Thicker gloves (up to 3 mm or more) may be required where there is a mechanical (as well as a chemical) risk i.e. where there is abrasion or puncture potential <p>Gloves must only be worn on clean hands. After using gloves, hands should be washed and dried thoroughly. Application of a non-perfumed moisturiser is recommended.</p> <ul style="list-style-type: none"> ▶ Rubber gloves (nitrile or low-protein, powder-free latex, latex/ nitrile). Employees allergic to latex gloves should use nitrile gloves in preference.

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	<ul style="list-style-type: none"> ▶ Double gloving should be considered. ▶ PVC gloves. ▶ Change gloves frequently and when contaminated, punctured or torn. ▶ Wash hands immediately after removing gloves. ▶ Protective shoe covers. [AS/NZS 2210] ▶ Head covering. <p>Experience indicates that the following polymers are suitable as glove materials for protection against undissolved, dry solids, where abrasive particles are not present.</p> <ul style="list-style-type: none"> ▶ polychloroprene. ▶ nitrile rubber. ▶ butyl rubber. ▶ fluorocautchouc. ▶ polyvinyl chloride. <p>Gloves should be examined for wear and/ or degradation constantly.</p>
Body protection	See Other protection below
Other protection	<ul style="list-style-type: none"> ▶ Employees working with confirmed human carcinogens should be provided with, and be required to wear, clean, full body protective clothing (smocks, coveralls, or long-sleeved shirt and pants), shoe covers and gloves prior to entering the regulated area. [AS/NZS ISO 6529:2006 or national equivalent] ▶ Employees engaged in handling operations involving carcinogens should be provided with, and required to wear and use half-face filter-type respirators with filters for dusts, mists and fumes, or air purifying canisters or cartridges. A respirator affording higher levels of protection may be substituted. [AS/NZS 1715 or national equivalent] ▶ Emergency deluge showers and eyewash fountains, supplied with potable water, should be located near, within sight of, and on the same level with locations where direct exposure is likely. ▶ Prior to each exit from an area containing confirmed human carcinogens, employees should be required to remove and leave protective clothing and equipment at the point of exit and at the last exit of the day, to place used clothing and equipment in impervious containers at the point of exit for purposes of decontamination or disposal. The contents of such impervious containers must be identified with suitable labels. For maintenance and decontamination activities, authorized employees entering the area should be provided with and required to wear clean, impervious garments, including gloves, boots and continuous-air supplied hood. ▶ Prior to removing protective garments the employee should undergo decontamination and be required to shower upon removal of the garments and hood. ▶ For quantities up to 500 grams a laboratory coat may be suitable. ▶ For quantities up to 1 kilogram a disposable laboratory coat or coverall of low permeability is recommended. Coveralls should be buttoned at collar and cuffs. ▶ For quantities over 1 kilogram and manufacturing operations, wear disposable coverall of low permeability and disposable shoe covers. ▶ For manufacturing operations, air-supplied full body suits may be required for the provision of advanced respiratory protection. ▶ Eye wash unit. ▶ Ensure there is ready access to an emergency shower. ▶ For Emergencies: Vinyl suit

Respiratory protection

Type -P Filter of sufficient capacity. (AS/NZS 1716 & 1715, EN 143:2000 & 149:2001, ANSI Z88 or national equivalent)

- Respirators may be necessary when engineering and administrative controls do not adequately prevent exposures.
- The decision to use respiratory protection should be based on professional judgment that takes into account toxicity information, exposure measurement data, and frequency and likelihood of the worker's exposure - ensure users are not subject to high thermal loads which may result in heat stress or distress due to personal protective equipment (powered, positive flow, full face apparatus may be an option).
- Published occupational exposure limits, where they exist, will assist in determining the adequacy of the selected respiratory protection. These may be government mandated or vendor recommended.
- Certified respirators will be useful for protecting workers from inhalation of particulates when properly selected and fit tested as part of a complete respiratory protection program.
- Where protection from nuisance levels of dusts are desired, use type N95 (US) or type P1 (EN143) dust masks. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU)
- Use approved positive flow mask if significant quantities of dust becomes airborne.
- Try to avoid creating dust conditions.

Where significant concentrations of the material are likely to enter the breathing zone, a Class P3 respirator may be required.

Class P3 particulate filters are used for protection against highly toxic or highly irritant particulates.

Filtration rate: Filters at least 99.95% of airborne particles

Suitable for:

- Relatively small particles generated by mechanical processes eg. grinding, cutting, sanding, drilling, sawing.
- Sub-micron thermally generated particles e.g. welding fumes, fertilizer and bushfire smoke.
- Biologically active airborne particles under specified infection control applications e.g. viruses, bacteria, COVID-19, SARS
- Highly toxic particles e.g. Organophosphate Insecticides, Radionuclides, Asbestos

Note: P3 Rating can only be achieved when used with a Full Face Respirator or Powered Air-Purifying Respirator (PAPR). If used with any other respirator, it will only provide filtration protection up to a P2 rating.

SECTION 9 Physical and chemical properties

Information on basic physical and chemical properties

Appearance	Peach/ yellow/ pink colour, round or oval shape, biconvex, beveled edge film coated tablet, debossed (TC) on one side and plain on other side; insoluble in water.		
Physical state	Divided Solid	Relative density (Water = 1)	Not Available
Odour	Not Available	Partition coefficient n-octanol / water	Not Available
Odour threshold	Not Available	Auto-ignition temperature (°C)	Not Applicable
pH (as supplied)	Not Applicable	Decomposition temperature (°C)	Not Available
Melting point / freezing point (°C)	Not Available	Viscosity (cSt)	Not Applicable
Initial boiling point and boiling range (°C)	Not Applicable	Molecular weight (g/mol)	Not Applicable
Flash point (°C)	Not Applicable	Taste	Not Available
Evaporation rate	Not Available	Explosive properties	Not Available
Flammability	Not Applicable	Oxidising properties	Not Available

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Upper Explosive Limit (%)	Not Applicable	Surface Tension (dyn/cm or mN/m)	Not Applicable
Lower Explosive Limit (%)	Not Applicable	Volatile Component (%vol)	Not Available
Vapour pressure (kPa)	Not Applicable	Gas group	Not Available
Solubility in water	Immiscible	pH as a solution (1%)	Not Applicable
Vapour density (Air = 1)	Not Available	VOC g/L	Not Available
Heat of Combustion (kJ/g)	Not Available	Ignition Distance (cm)	Not Available
Flame Height (cm)	Not Available	Flame Duration (s)	Not Available
Enclosed Space Ignition Time Equivalent (s/m ³)	Not Available	Enclosed Space Ignition Deflagration Density (g/m ³)	Not Available

SECTION 10 Stability and reactivity

Reactivity	See section 7
Chemical stability	<ul style="list-style-type: none"> ▶ Unstable in the presence of incompatible materials. ▶ Product is considered stable. ▶ Hazardous polymerisation will not occur.
Possibility of hazardous reactions	See section 7
Conditions to avoid	See section 7
Incompatible materials	See section 7
Hazardous decomposition products	See section 5

SECTION 11 Toxicological information

Information on toxicological effects

a) Acute Toxicity	There is sufficient evidence to classify this material as acutely toxic.
b) Skin Irritation/Corrosion	There is sufficient evidence to classify this material as skin corrosive or irritating.
c) Serious Eye Damage/Irritation	There is sufficient evidence to classify this material as eye damaging or irritating
d) Respiratory or Skin sensitisation	There is sufficient evidence to classify this material as sensitising to skin or the respiratory system
e) Mutagenicity	There is sufficient evidence to classify this material as mutagenic
f) Carcinogenicity	Based on available data, the classification criteria are not met.
g) Reproductivity	There is sufficient evidence to classify this material as toxic to reproductivity
h) STOT - Single Exposure	There is sufficient evidence to classify this material as toxic to specific organs through single exposure
i) STOT - Repeated Exposure	There is sufficient evidence to classify this material as toxic to specific organs through repeated exposure
j) Aspiration Hazard	Based on available data, the classification criteria are not met.

Inhaled	<p>Evidence shows, or practical experience predicts, that the material produces irritation of the respiratory system, in a substantial number of individuals, following inhalation. In contrast to most organs, the lung is able to respond to a chemical insult by first removing or neutralising the irritant and then repairing the damage. The repair process, which initially evolved to protect mammalian lungs from foreign matter and antigens, may however, produce further lung damage resulting in the impairment of gas exchange, the primary function of the lungs. Respiratory tract irritation often results in an inflammatory response involving the recruitment and activation of many cell types, mainly derived from the vascular system.</p> <p>Cellulose, after a single intratracheal dose (15 mg per animal) brought about fibrosing granulomatous bronchioloalveolitis and an increase of IgA production in the bronchioalveolar lavage. Fibrosing alveolitis showed moderate progression as a function of time. Injury of Type I pneumocytes and incomplete repair of Type II pneumocytes were detected. The damage of alveolar epithelium initiated and activated a series of processes that led to definite pulmonary alterations and pulmonary fibrosis leading to disintegration of the alveolo-capillary morphological functional unit.</p> <p>Tatrai, E. et al: Journal of Applied Toxicology; 16(2) 129-135 (1996)</p> <p>Some health effects associated with wood, cotton, flax, jute and hemp particles or fibres are not attributable to cellulose content but to other substances and/or impurities.</p> <p>Persons with impaired respiratory function, airway diseases and conditions such as emphysema or chronic bronchitis, may incur further disability if excessive concentrations of particulate are inhaled.</p> <p>If prior damage to the circulatory or nervous systems has occurred or if kidney damage has been sustained, proper screenings should be conducted on individuals who may be exposed to further risk if handling and use of the material result in excessive exposures.</p> <p>Inhalation of vapours or aerosols (mists, fumes), generated by the material during the course of normal handling, may be damaging to the health of the individual.</p>
Ingestion	Accidental ingestion of the material may be harmful; animal experiments indicate that ingestion of less than 150 gram may be fatal or may produce serious damage to the health of the individual.
Skin Contact	<p>Evidence exists, or practical experience predicts, that the material either produces inflammation of the skin in a substantial number of individuals following direct contact, and/or produces significant inflammation when applied to the healthy intact skin of animals, for up to four hours, such inflammation being present twenty-four hours or more after the end of the exposure period. Skin irritation may also be present after prolonged or repeated exposure; this may result in a form of contact dermatitis (nonallergic). The dermatitis is often characterised by skin redness (erythema) and swelling (oedema) which may progress to blistering (vesiculation), scaling and thickening of the epidermis. At the microscopic level there may be intercellular oedema of the spongy layer of the skin (spongiosis) and intracellular oedema of the epidermis.</p> <p>The material may accentuate any pre-existing dermatitis condition</p> <p>Open cuts, abraded or irritated skin should not be exposed to this material</p> <p>Entry into the blood-stream through, for example, cuts, abrasions, puncture wounds or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected.</p>
Eye	When applied to the eye(s) of animals, the material produces severe ocular lesions which are present twenty-four hours or more after instillation.
Chronic	Repeated or long-term occupational exposure is likely to produce cumulative health effects involving organs or biochemical systems. Long-term exposure to respiratory irritants may result in disease of the airways involving difficult breathing and related systemic problems.

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Strong evidence exists that the substance may cause irreversible but non-lethal mutagenic effects following a single exposure. Practical evidence shows that inhalation of the material is capable of inducing a sensitisation reaction in a substantial number of individuals at a greater frequency than would be expected from the response of a normal population. Pulmonary sensitisation, resulting in hyperactive airway dysfunction and pulmonary allergy may be accompanied by fatigue, malaise and aching. Significant symptoms of exposure may persist for extended periods, even after exposure ceases. Symptoms can be activated by a variety of nonspecific environmental stimuli such as automobile exhaust, perfumes and passive smoking. Practical experience shows that skin contact with the material is capable either of inducing a sensitisation reaction in a substantial number of individuals, and/or of producing a positive response in experimental animals. Substances that can cause occupational asthma (also known as asthmagens and respiratory sensitisers) can induce a state of specific airway hyper-responsiveness via an immunological, irritant or other mechanism. Once the airways have become hyper-responsive, further exposure to the substance, sometimes even to tiny quantities, may cause respiratory symptoms. These symptoms can range in severity from a runny nose to asthma. Not all workers who are exposed to a sensitiser will become hyper-responsive and it is impossible to identify in advance who are likely to become hyper-responsive. Substances that can cause occupational asthma should be distinguished from substances which may trigger the symptoms of asthma in people with pre-existing air-way hyper-responsiveness. The latter substances are not classified as asthmagens or respiratory sensitisers. Wherever it is reasonably practicable, exposure to substances that can cause occupational asthma should be prevented. Where this is not possible the primary aim is to apply adequate standards of control to prevent workers from becoming hyper-responsive. Activities giving rise to short-term peak concentrations should receive particular attention when risk management is being considered. Health surveillance is appropriate for all employees exposed or liable to be exposed to a substance which may cause occupational asthma and there should be appropriate consultation with an occupational health professional over the degree of risk and level of surveillance.

Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed. Serious damage (clear functional disturbance or morphological change which may have toxicological significance) is likely to be caused by repeated or prolonged exposure. As a rule the material produces, or contains a substance which produces severe lesions. Such damage may become apparent following direct application in subchronic (90 day) toxicity studies or following sub-acute (28 day) or chronic (two-year) toxicity tests.

Exposure to the material may cause concerns for humans owing to possible developmental toxic effects, generally on the basis that results in appropriate animal studies provide strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of other toxic effects.

There is some evidence to provide a presumption that human exposure to the material may result in impaired fertility on the basis of: some evidence in animal studies of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of other toxic effects.

Common adverse drug reactions (ADRs) Angiotensin II receptor antagonists (angiotensin receptor blockers - ARBs), include: dizziness, headache, and/or hyperkalemia. Infrequent adverse drug reactions (ADRs) associated with therapy include: first dose orthostatic hypotension, rash, diarrhoea, dyspepsia, abnormal liver function, muscle cramp, myalgia, back pain, insomnia, decreased haemoglobin levels, renal impairment, pharyngitis, and/or nasal congestion.

Other reported adverse effects include liver problems and effects on the fetus.

Kidney problems may occur with all angiotensin-converting enzyme (ACE) inhibitors that directly follows from their mechanism of action. High blood potassium is another possible complication of treatment with an ACE inhibitor due to its effect on aldosterone. Suppression of angiotensin II leads to a decrease in aldosterone levels. Since aldosterone is responsible for increasing the excretion of potassium, ACE inhibitors can cause retention of potassium. Some people, however, can continue to lose potassium while on an ACE inhibitor. Hyperkalemia may decrease the velocity of impulse conduction in the nerves and muscles, including cardiac tissues. This leads to cardiac dysfunction and neuromuscular consequences, such as muscle weakness, paresthesia, nausea, diarrhea, and others. Close monitoring of potassium levels is required in patients receiving treatment with ACE inhibitors who are at risk of hyperkalemia.

Another possible adverse effect specific for ACE inhibitors, but not for other renin-angiotensin-aldosterone system (RAAS) blockers, is an increase in bradykinin level.

A persistent dry cough is a relatively common adverse effect believed to be associated with the increases in bradykinin levels produced by ACE inhibitors, although the role of bradykinin in producing these symptoms has been disputed. Many cases of cough in people on ACE inhibitors may not be from the medication itself, however. People who experience this cough are often switched to angiotensin II receptor antagonists.

Some (0.7%) develop angioedema due to increased bradykinin levels. A genetic predisposition may exist. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, administer appropriate therapy.

A severe rare allergic reaction can affect the bowel wall and secondarily cause abdominal pain.

Hematologic effects, such as neutropenia, agranulocytosis and other blood dyscrasias, have occurred during therapy with ACE inhibitors, especially in people with additional risk factors

While one of the main rationales for the use of angiotensin II receptor antagonists is the avoidance of dry cough and/or angioedema associated with ACE inhibitor therapy, these may still occur on rare occasions. In addition, there is also a small risk of cross-reactivity in patients having experienced angioedema with ACE inhibitor therapy.

The use of drugs that directly act on the renin-angiotensin system can cause foetal and neonatal morbidity and death.

In pregnant women. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios (low amniotic fluid level) can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

ACE inhibitors taken during all the trimesters have been reported to cause congenital malformations, stillbirths, and neonatal deaths.

Commonly reported fetal abnormalities include hypotension, renal dysplasia, anuria/oliguria, oligohydramnios, intrauterine growth retardation, pulmonary hypoplasia, patent ductus arteriosus, and incomplete ossification of the skull. Overall, about half of newborns exposed to ACE inhibitors are adversely affected, leading to birth defects.

In pregnancy during the second and third trimesters, ACE inhibitors may cause injury and even death to the developing foetus. Neonatal hypotension, renal failure, skull hypoplasia, oligohydramnios (insufficient amounts of amniotic fluid), associated with foetal limb contractures, craniofacial malformations, hypoplastic lung development and intra-uterine growth retardation, have been reported. It is not known whether exposure limited to the first trimester produces adverse foetal outcomes. Exposure in utero may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have been associated with foetal death in utero.

Myocardial infarction: the controversy

The issue of whether angiotensin II receptor antagonists slightly increase the risk of myocardial infarction (MI or heart attack) is currently being investigated. Some studies suggest ARBs can increase the risk of MI. However, other studies have found ARBs do not increase the risk of MI. To date, with no consensus on whether ARBs have a tendency to increase the risk of myocardial infarction, further investigations are underway.

Indeed, as a consequence of AT1 blockade, ARBs increase angiotensin II levels several-fold above baseline by uncoupling a negative-feedback loop. Increased levels of circulating angiotensin II result in unopposed stimulation of the AT2 receptors, which are, in addition, upregulated. However, some data suggests AT2 receptor stimulation may be less beneficial than previously proposed, and may even be harmful under certain circumstances through mediation of growth promotion, fibrosis, and hypertrophy, as well as eliciting proatherogenic and proinflammatory effects.

Cancer risk factors

A study published in 2010 determined that "...meta-analysis of randomised controlled trials suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis. Given the limited data, it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug. These findings warrant further investigation." A later meta-analysis by the FDA of 31 randomized controlled trials comparing ARBs to other treatment found no evidence of an increased risk of incident (new) cancer, cancer-related death, breast cancer, lung cancer, or prostate cancer in patients receiving ARBs. In 2013, comparative effectiveness research from the United States Department of Veterans Affairs on the experience of more than a million Veterans found no increased risks for either lung cancer

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(original article in Journal of Hypertension) or prostate cancer (original article in The Journal of Clinical Pharmacology). The researchers concluded "In this large nationwide cohort of United States Veterans, we found no evidence to support any concern of increased risk of lung cancer among new users of ARBs compared with nonusers. Our findings were consistent with a protective effect of ARBs."

In May 2013, a senior regulator at the Food & Drug Administration, Medical Team Leader Thomas A. Marciniak, revealed publicly that contrary to the FDA's official conclusion that there was no increased cancer risk, after a patient by patient examination of the available FDA data he had concluded that there was a lung-cancer risk increase of about 24% in ARB patients, compared with patients taking a placebo or other drugs. One of the criticisms Marciniak made was that the earlier FDA meta-analysis did not count lung carcinomas as cancers. In ten of the eleven studies he examined, Marciniak said that there were more lung cancer cases in the ARB group than the control group. Ellis Unger, chief of the drug-evaluation division that includes Dr. Marciniak, was quoted as calling the complaints a "diversion," and saying in an interview, "We have no reason to tell the public anything new." In an article about the dispute, the Wall Street Journal interviewed three other doctors to get their views; one had "no doubt" ARBs increased cancer risk, one was concerned and wanted to see more data, and the third thought there was either no relationship or a hard to detect, low-frequency relationship

Lithium:

Increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists.

Combination Blockade Of The Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The cellulose derivatives pass essentially unchanged through the gastrointestinal tract following oral administration to rats, dogs and man.

Acute, subchronic, chronic toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity studies of cellulose derivatives indicated that they are practically non-toxic when administered by oral, intraperitoneal, subcutaneous or dermal routes. While no clinical inhalation studies have been conducted, long term exposure to the dusts of cellulose ethers in manufacturing operations has not lead to any significant adverse effects. Ocular and dermal irritation studies indicate that the cellulose derivatives are, at most, minimally irritating and are not dermal sensitizers. Clinical studies confirm these results.

Amended Safety Assessment of Cellulose and Related Polymers as used in Cosmetics: Final Report of the Cosmetic Ingredient Review (CIR) Expert Panel: March 2009

Inhalation studies indicate that cellulose fibres may be fibrogenic; this finding continues to be the subject of extensive research. Cellulose is not considered an inert substance because :

- in rats, it causes granulomatous fibrosing alveolitis at the end of the third month after exposure,
- in rats there was an increase in the secretion of plasminogen activator and interleukin 1 as well as the release of lactate dehydrogenase from macrophages, in a manner similar to asbestos,
- there were increases in the incidence of obstructive lung diseases and bronchial asthma in humans at work and in the residential environment where exposure to cellulose was common,
- the substance may induce free radical production in human leucocytes.

Byssinosis is an occupational disease of the lungs caused by inhalation of cotton dust or dusts from other vegetable fibres such as flax, hemp, or sisal. Byssinosis is a chronic, asthma-like narrowing of the airways. Also called brown lung disease, byssinosis occurs almost exclusively in people who work with unprocessed cotton.

Cotton dust disease, "byssinosis", is well known among cotton mill workers. Cotton dust consists largely of cellulose fibre. Exposure to two components of the total dust, the "respirable" and "medium" fraction correlated significantly with the prevalence of respiratory symptoms.

Inhalation exposure to a concentration of 0.3 to 0.4 mg/m³ of "fly-free" dust results in a 20% occurrence of byssinosis. "Fly-free" dust is the sum of respirable and medium-length fibres. At 0.46 mg/m³, Grade II byssinosis occurs. A byssinosis (all grades) prevalence of 20%, at 0.3 mg/m³ occurs when the fibre length is less than 15 µm (aerodynamic equivalent diameter). Byssinosis is not caused by mechanical irritation but by reactions caused by pharmacologically active substances producing oedema or contraction of the smooth musculature of the airways. The causative agent is suspected to be an endotoxin, in turn, thought to be a cell wall component of bacteria found in cotton. Symptoms of byssinosis include chest tightness, wheezing and dyspnoea. Symptoms usually appear after an absence from work and may subside after 2-days of exposure. As the disease progresses, symptoms may persist for longer periods until they are constant. The individual may eventually exhibit chronic bronchitis and emphysema. Increased physical exertion may produce shortness of breath.

Repeated ingestion of sulfonamides used for therapeutic purposes has caused nausea, vomiting, abdominal pain, diarrhoea, anorexia, stomatitis, impaired folic acid absorption, exacerbation of porphyria, acidosis, liver injury with jaundice and hypoprothrombinemia, and pancreatitis. Hepatitis has been reported and may be fatal. Renal effects are often prominent and may include crystalluria, haematuria, proteinuria, pain and frequent urination, necrosis of the tubules, nephritic syndrome, and toxic necrosis with oliguria or anuria with azotemia. Neurologic effects include headache, drowsiness, insomnia, vertigo, tinnitus, hearing loss, mental depression, hallucinations, ataxia, muscular paralysis, peripheral neuropathy, transient lesions of the posterior spinal column, transverse myelitis, convulsions and unconsciousness. Haematological effects include eosinophilia, thrombocytopenia, leukopenia, neutropenia, agranulocytosis, pancytopenia, megoblastic anaemia, Heinz body anaemia and aplastic anaemia; petechiae and purpura may result. Acute haemolytic anaemia may also result (possibly as a result of hypersensitivity reactions) with people of African descent apparently more susceptible than Europeans - glucose-6-phosphate deficiency also appears to be a factor. Methaemoglobinemia and cyanosis may also occur. Ocular effects may include acute transient myopia, keratitis and conjunctivitis with inflammation and chemosis accompanied by swelling of the lids and in more severe cases, photophobia. Cross-sensitivity amongst the sulfonamides is common and allergic reaction may occur following systemic use or topical application. Sensitisation may produce generalised skin eruptions, urticaria and pruritus. Stevens-Johnson syndrome; a severe form of erythema multiforme associated with wide-spread lesions of the skin, mucous membranes and which may be fatal in about 25% of cases, has occurred in patients treated with sulfonamides. This syndrome may produce conjunctival and corneal scarring, serum sickness, periorbital oedema, angioedema, arthritis, arthralgia, allergic myocarditis, decreased pulmonary function and eosinophilic pneumonia. Other effects of long-term therapy include fever, chills, alopecia, vasculitis, lupus erythematosus, oligospermia, infertility, hypothyroidism and on occasion, goiter and diuresis.

More severe responses to treatment include irreversible neuromuscular and central nervous system changes and fibrosing alveolitis. During sulfonamide treatment, direct exposure to sunlight should be avoided as photosensitisation dermatitis may develop. This form of phototoxic dermatitis may be contrasted to photoallergic dermatitis produced by specific sensitising agents through immunological intervention. Phototoxic reactions have been described following contact, ingestion or injection of causal agents. The chemical may reach the skin by the circulatory system following ingestion or following parenteral administration. The actual skin changes vary with the agent and circumstances of the exposure. Swelling and redness (erythema) frequently occur, and blistering may also result; increased skin temperature and pruritus may follow. This is analogous to irritant contact dermatitis and occurs immediately following contact.

Hyperpigmentation may also follow the reaction. Photodermatitis of this type requires activation of a chemical substance on the skin surface by UV radiation (290 to 490 nm wavelength) for its clinical expression. In all cases, inflammation develops on the body surfaces normally exposed to sunlight (dorsal hands, arms, neck, face), provided that the responsible photosensitiser also contacts the anatomic areas. Covered skin, the eyelids, submental chin and upper ears covered by hair, are characteristically spared. Phototoxic reactions, analogous to irritant contact dermatitis, are typically accompanied by immediate burning, stinging or "smarting" of the skin shortly following sun exposure, and clinical inflammation appears more like an acute sunburn than an eczematous dermatitis. Photoallergic dermatitis may result from contact with the material; this is characterised by an increased reactivity of the skin to ultra-violet (UV) and/or visible radiation produced by a chemical agent on an immunological basis and occurs after a latent period of days or months. This type of response can be elicited only in individuals who have been previously allergically sensitised to the chemical agent and appropriate radiation.

Photoallergic dermatitis is relatively rare (certainly more so than phototoxic dermatitis produced by non-immunological principals) and presents, clinically, as an eczematous dermatitis in sun-exposed areas (distinguishing it from phototoxic dermatitis which is analogous to contact irritant dermatitis and produces swelling, redness and even blistering); photoallergic dermatitis may eventually spread to areas covered by clothes. Lichenification (thickening with increased skin markings) and chronic pigmentary changes may also develop.

Photoallergic reactions may sometimes be followed by a persistent state of light reactivity (persistent light reactor) where clinical dermatitis recurs following exposure to sunlight alone, in the absence of the original initiating chemical. Studies in rats have shown that long-term administration of sulfonamides may produce thyroid malignancies; rats, however, appear to be more susceptible to the goiterogenic effects of sulfonamides than do other animal species. Sulfonamides may cause kernicterus in the neonate and their use is not recommended during

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pregnancy. Studies in rats and mice given high oral doses have shown that certain sulfonamides cause a significant incidence of cleft palate and other bony abnormalities in the foetus.

The synthetic, amorphous silicas are believed to represent a very greatly reduced silicosis hazard compared to crystalline silicas and are considered to be nuisance dusts.

When heated to high temperature and a long time, amorphous silica can produce crystalline silica on cooling. Inhalation of dusts containing crystalline silicas may lead to silicosis, a disabling pulmonary fibrosis that may take years to develop. Discrepancies between various studies showing that fibrosis associated with chronic exposure to amorphous silica and those that do not may be explained by assuming that diatomaceous earth (a non-synthetic silica commonly used in industry) is either weakly fibrogenic or nonfibrogenic and that fibrosis is due to contamination by crystalline silica content

Some workers may develop chronic occupational dermatitis (generally mild) through the handling of starch products.

When starch is used as a lubricant in surgical gloves, small amounts, released into the patient during the course of surgery, have resulted in granulomas and peritonitis.

Studies indicate that diets containing large amounts of non-absorbable polysaccharides, such as cellulose, might decrease absorption of calcium, magnesium, zinc and phosphorus.

Polysaccharides are polymeric carbohydrates that consist of monosaccharide units, which are connected together with glycosidic bonds.

Due to the structural variation of different monosaccharides as well as the innumerable ways that these building blocks link with each other, polysaccharides can be considered as structurally complex biomacromolecules. Polysaccharides originating from plants (e.g., starch and guar gum), microbes (e.g., xanthan), algae (e.g., alginates and carrageenans) and animals (e.g., glycogen and chitin) are frequently used in food. Starch, a high molar mass compound consisting of (1->4)-linked alpha-D-glucopyranosyl units, is an important energy nutrient that is abundant in common foods, such as cereals and root crops. Although many other food polysaccharides are not digested in the upper gastrointestinal tract of humans, they often serve functions other than being components giving nutritional value. For example, plant cell-wall polysaccharides, such as arabinoxylans and beta-glucan, exist in cereal-based foods, and "plant gums" are used as thickeners, emulsifiers, emulsion stabilizers, gelling agents and encapsulating agents. These non-digestible polysaccharides are important for health because they are considered as dietary fibre, which promote colon health, regulate post-prandial blood glucose levels and reduce serum cholesterol levels.

Despite the fact that nature provides various sources of polysaccharides, and that scientific research on their exploitation as food materials is increasingly active, a relatively low number of polysaccharides are authorized for use as food ingredients. For example, in the European Union (EU) and in Switzerland, among the permitted food additives (identified by an E number) only a small percentage are polysaccharide-based (native or structurally modified). The difference between other food ingredients and food additives is mainly the quantity used in any given product. Food ingredients can be consumed alone as food (e.g., starch), whereas food additives (e.g., carboxymethyl cellulose) are used in small quantities (usually less than 2%) relative to the total food composition but they, nonetheless, play an important role in the food products. Regarding food additive use in Europe, the European Food Safety Authority (EFSA) has an expert Panel on Food Additives and Nutrient Sources Added to Food (ANS), which evaluates the safety of food additives. Similarly, if new ingredients are released into the market, EFSA's Panel on Dietetic Products, Nutrition and Allergies (NDA) has the responsibility of evaluating the safety of Novel Food ingredients

The vast majority of polysaccharides used as food ingredients are plant-based. In addition to the cellulosic polysaccharides, other types of food-grade ingredients or additives, such as, vanillin aroma, glycerol esters of wood rosins (E445), xylitol (E967) and steryls/stanols, are derived from wood. The main components of wood are polysaccharides: cellulose (40–50 wt%) and hemicelluloses (20–35%), while lignin comprises 15–30% of wood mass.

The material contains a substantial proportion of a polymer considered to be of low concern (PLC). The trend towards production of lower molecular weight polymers (thus reducing the required level of solvent use and creating a more "environmentally-friendly" material) has brought with it the need to define PLCs as those

having molecular weights of between 1000 and 10000 and containing less than 10% of the molecules with molecular weight below 500 and less than 25% of the molecules with a molecular weight below 1000. These may contain unlimited low concern functional groups or moderate concern reactive functional groups with a combined functional group equivalent weight (FGEW, a concept developed by the US EPA describing whether the reactive functional group is sufficiently diluted by polymeric material) of a 1000 or more (provided no high concern groups are present) or high concern reactive functional groups with a FGEW of 5000 or more (FGEW includes moderate concern groups if present).

having molecular weights exceeding 10000 (without restriction on reactive groups).

Inhalation of polymers with molecular weights > 70,000 Da has been linked with irreversible lung damage due to lung overloading and impaired clearance of particles from the lung, particularly following repeated exposure. If the polymer is inhaled at low levels and/or infrequently, it is assumed that it will be cleared from the lungs.

Reactive functional groups are in turn classified as being of low, moderate or high concern. Classification of the polymer as a PLC, in accordance with established criteria, does not mean that hazards will not be associated with the polymer (during its import, manufacture, use, storage, handling or disposal). The polymer may, for example, contain a large number of particles in the respirable range, a hazard which may need to be assessed in the health and safety risk assessment. Similarly a polymer with low concern reactive may be released into the environment in large quantities and produce an environmental hazard.

Whilst it is generally accepted that polymers with a molecular weight exceeding 1000 are unlikely to pass through biological membranes, oligomers with lower molecular weight and specifically, those with a molecular weight below 500, may. Estimations based on a "highly" dispersed polymer population (polydispersity = 10) suggests that the molecular weight of the polymer carrying a reactive group of high concern must be 5000 to be considered a PLC; similarly a polymer of approximate molecular weight 1000 could contain no more than one reactive group of moderate concern (for two moderate concern groups, the molecular weight would be about 2500).

Repeated exposure to synthetic amorphous silicas may produce skin dryness and cracking.

Available data confirm the absence of significant toxicity by oral and dermal routes of exposure.

Numerous repeated-dose, subchronic and chronic inhalation toxicity studies have been conducted in a number of species, at airborne concentrations ranging from 0.5 mg/m³ to 150 mg/m³. Lowest-observed adverse effect levels (LOAELs) were typically in the range of 1 to 50 mg/m³. When available, the no-observed adverse effect levels (NOAELs) were between 0.5 and 10 mg/m³. Differences in values may be due to particle size, and therefore the number of particles administered per unit dose. Generally, as particle size diminishes so does the NOAEL/LOAEL. Exposure produced transient increases in lung inflammation, markers of cell injury and lung collagen content. There was no evidence of interstitial pulmonary fibrosis.

In general, vasodilators dilate or prevent constriction of the blood vessels, which allow greater blood flow to various organs in the body. Many vasodilators bind to receptors on endothelial cells of the blood vessel, which stimulate calcium release. Calcium activates the enzyme nitric oxide synthase (NO synthase) and converts L-arginine into NO. It leaves the endothelial cell via diffusion and enters vascular smooth muscle cells. NO activates GTP and converts it into cGMP. cGMP then stimulates myosin-light chain phosphatase, which removes a single phosphate from myosin and actin filaments. The dephosphorylation of myosin and actin filaments allows vascular smooth muscle relaxation. Direct-acting vasodilating agents enter the vascular smooth muscle cell to cause vasodilatation. For long term treatment of hypertension, the use of these drugs as monotherapy is accompanied by activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. These counteracting mechanisms limit the antihypertensive efficacy of these drugs, and cause adverse effects such as tachycardia and fluid retention. These adverse effects require treatment with beta-blockers and diuretics. However, there is still an important role for intravenous vasodilator therapy in hypertensive emergencies. In the treatment of chronic heart failure, vasodilator therapy has been an important advance. Combination therapy with hydralazine and nitrates is efficacious in improving survival, but ACE inhibitors have an incremental benefit on survival over this combination.

Undertreatment and/or non-compliance, using vasodilation therapies, can cause severe hypertension, and this can lead to catastrophic events such as stroke, hypertensive emergency, aortic dissection, and many other preventable diseases

Long term exposure to high dust concentrations may cause changes in lung function (i.e. pneumoconiosis) caused by particles less than 0.5 micron penetrating and remaining in the lung. A prime symptom is breathlessness. Lung shadows show on X-ray.

Therapeutic effects caused by long-term use of calcium channel blocking agents include cardiovascular effects such as peripheral oedema, rebound vasospasm, palpitation, congestive heart failure, tachycardia, hypertension, and abnormal ECG. Other effects may include neurological deficits, headache, vomiting, diarrhoea, abdominal discomfort, gastrointestinal haemorrhage, hepatitis and jaundice, dermatitis, acne, itching, anaemia, thrombocytopenia and a disseminated intravascular coagulation. Haematoma and deep vein thrombosis may occur.

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On the basis, primarily, of animal experiments, concern has been expressed that the material may produce carcinogenic or mutagenic effects; in respect of the available information, however, there presently exists inadequate data for making a satisfactory assessment.

Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide Tablets	TOXICITY	IRRITATION
	Not Available	Not Available
cellulose	TOXICITY	IRRITATION
	Dermal (rabbit) LD50: >2000 mg/kg ^[2]	Not Available
	Inhalation (Rat) LC50: >5.8 mg/L4h ^[2]	
	Oral (Rat) LD50: >5000 mg/kg ^[2]	
starch	TOXICITY	IRRITATION
	Not Available	Skin (Human): 300ug/3D (intermittent) - Mild
olmesartan medoxomil	TOXICITY	IRRITATION
	Oral (Rat) LD50: >2000 mg/kg ^[2]	Not Available
hydrochlorothiazide	TOXICITY	IRRITATION
	Oral (Mouse) LD50: 1175 mg/kg ^[2]	Not Available
amlodipine besylate	TOXICITY	IRRITATION
	Oral (Mouse) LD50: 37 mg/kg ^[2]	Not Available
talc	TOXICITY	IRRITATION
	dermal (rat) LD50: >2000 mg/kg ^[1]	Eye: no adverse effect observed (not irritating) ^[1]
	Inhalation (Rat) LC50: >2.1 mg/14h ^[1]	Skin (Human): 300ug/3D (intermittent) - Mild
	Oral (Rat) LD50: >5000 mg/kg ^[1]	Skin: no adverse effect observed (not irritating) ^[1]

Legend: 1. Value obtained from Europe ECHA Registered Substances - Acute toxicity 2. Value obtained from manufacturer's SDS. Unless otherwise specified data extracted from RTECS - Register of Toxic Effect of chemical Substances

STARCH	The material may cause skin irritation after prolonged or repeated exposure and may produce on contact skin redness, swelling, the production of vesicles, scaling and thickening of the skin.
OLMESARTAN MEDOXOMIL	<p>For G-protein inhibitors/ antagonists/ modulators.</p> <p>G protein-coupled receptors (GPCRs) are essential cell membrane signaling molecules and represent the most important class of drug targets. Some signaling pathways downstream of a GPCR may be responsible for drug adverse effects, while others mediate therapeutic efficacy. Biased ligands preferentially activate only a subset of all GPCR signaling pathways. They hold great potential to become next-generation GPCR drugs with less side effects due to their potential to exclusively activate desired signaling pathways.</p> <p>GPCR ligands include odorants, tastants, and neurotransmitters, and vary in size and properties. Dramatic chemical diversity may occur even among ligands of the same receptor. Chemical variability of antagonists significantly correlates with the binding site hydrophobicity and anti-correlates with the number of hydrogen bond donors in the binding site. The number of disulfide bridges in the extracellular region of a receptor anti-correlates with the range of molecular weights of its antagonists, highlighting the role of the entrance pathway in determining the size selectivity for GPCR antagonists.</p> <p>The number of protein targets included in the cross-pharmacology profile of the different GPCRs changes significantly upon varying the ligand similarity and binding affinity criteria. However, with the exception of muscarinic receptors, aminergic GPCRs distinguish themselves from the rest of the members in the family by their remarkably high levels of pharmacological similarity among them.</p> <p>GPCRs are classified under the GRAFS system (Metabotropic Glutamate, Rhodopsin, Adhesion, Frizzled/taste2/Smoothed and Secretin), with therapies having been developed for about 30 GPCRs from the glutamate, rhodopsin and secretin families.</p> <p>GPCR signaling requires significant conformational changes within the trans-membrane TM domain, triggered by agonist binding, and is often coupled to interactions from the extracellular domains or loops. It is becoming clear that many binding sites and mechanisms exist for positive and negative allosteric regulation, and for biased signaling pathways, likely in greater numbers than seen in most other protein systems.</p> <p>When GPCRs are exposed to a neutral agonist, such as morphine on mu-opioid receptor, an occupied receptor can generate several signal waves (non-biased agonist). In GPCR signaling, the ability of a molecule to selectively activate one pathway without affecting another pathway is called biased agonism. Biased signaling occurs at different signaling proteins, including G proteins, GRKs, beta-arrestins, and even at levels of the allosteric binding site. Since GPCR activation-induced two distinct signal waves, G protein-dependent signaling followed by beta-arrestin-dependent signaling opens a new promising therapeutic future in the world of GPCRs. This is true since discovering such molecules dramatically lowers the adverse effects by turning off unwanted signals. For example, the analgesic effect of morphine (neutral agonist) through the activation of u-receptors is accompanied by several side effects, including constipation, respiratory depression, tolerance, nausea, and sedation.</p> <p>Despite the long history and obvious desirability of developing drugs targeting GPCRs, there are several problems associated with their development. For example, the muscarinic M1 receptor is a well-validated target for agonists that could alleviate cognitive decline during neurodegeneration.</p> <p>Muscarinic acetylcholine receptors (MRs, or mAChRs), which are more sensitive to muscarine than to nicotine, are a group of class A GPCRs comprising five distinct subtypes, named as muscarinic M1, M2, M3, M4, and M5 receptors (M1R-M5R) M1R, M3R, and M5R are coupled to the Gq/11 family of G proteins, whereas M2R and M4R are coupled to the Gi/o family of G proteins.</p> <p>However, the orthosteric binding site of M1 is virtually identical to those of the related receptors M2, M3, M4, and M5 as they all bind the native ligand acetylcholine, and activation of M2 and M3 in particular gives rise to dose-limiting side effects (gastrointestinal [GI] disturbances, cardiovascular effects).</p> <p>Atropine and other anticholinergic agents exert their bronchodilator effects through the blockade of MRs in the airways. As a tertiary ammonium derivative, atropine is a nonselective antagonist with similar affinity for all of the MR subtypes. The half-life of atropine for M3R residence is 3.5 hours. Although extensively used in the past, atropine is rarely used at the present time because it is well absorbed into the systemic circulation and penetrates the blood-brain barrier, leading to multiple systemic side effects, including tachycardia.</p> <p>Several long-acting muscarinic antagonists (LAMAs) are under investigation or are available for the treatment of obstructive airway diseases. LAMAs are considered to be safe drugs at recommended dosages. However, because MRs are expressed not only in the lungs, but also in the heart and the digestive and urinary tracts, the blockade of different MR subtypes in these organs by LAMA treatment can cause diverse, unwanted physiologic effects. For example, these agents can initially block prejunctional M2R on cholinergic airway nerves that normally reduce the release of the bronchoconstricting neurotransmitter acetylcholine, thus resulting in cough and paradoxical bronchoconstriction. Side effects including cardiovascular morbidity and mortality of inhaled LAMA agents in asthma need to be further studied and defined.</p>

Continued...

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	<p>Another potential source of side effects when targeting other receptors could arise due to signaling through multiple different pathways. There are multiple signaling pathways for GPCRs, and it is sometimes possible to bias the signaling of a given GPCR through either a specific G protein or through beta arrestin which could reduce the side effects of some drugs.</p> <p>Targeting G protein alpha-subunits has the potential for pleiotropic effects and could result in multiple side effects. Particular targets of concern include ion channels such as the G protein-activated inward rectifier K⁺ channel (GIRK) and the N-type voltage-gated calcium channels. Gbeta-gamma activates GIRK channels in neurons and in atria, leading to a hyperpolarization-induced decrease in action potential firing. Therefore, when considering the use of Gbeta-gamma inhibitors in cardiac or immune therapy, interfering with the regulation of action potentials would have highly undesirable side effects, such as arrhythmias. However, empirical data using prototypical Gbeta-gamma blockers indicate that these pathways are unaffected by Gbeta-gamma inhibitors, and animals treated with gallein show no signs of arrhythmias or alterations in heart rate.</p> <p>For olmesartan medoxomil</p> <p>Antigenicity tests Result: Negative Species: Guinea pig Antigenicity tests Result: Negative Species: Mouse Ames assay Result: Negative Chromosomal aberrations in cultured cells in vitro Result: Positive In vitro Syrian hamster embryo cell transformation assay Result: Negative Mouse bone marrow micronucleus test in vivo Result: Negative MutaMouse intestine and kidney in vivo Result: Negative Thymidine kinase mutations in in vitro mouse lymphoma assay Result: Positive</p> <p>Reproductive effects</p> <p>Maternal use during the second and third trimesters of pregnancy of drugs that act on the renin-angiotensin system has been associated with fetal and newborn injury and death. Adverse effects include growth retardation, incomplete lung development, skeletal deformities, and kidney damage.</p> <p>1 mg/kg/day Result: No malformations Species: Rabbit 1000 mg/kg/day Result: No increase in congenital anomalies Species: Rat Comments: Non-malforming toxicities such as decreased pup weight observed at maternal doses of 1.6 mg/kg/day * USP SDS</p> <p>In vitro Bacterial Mutagenicity (Ames) Salmonella Negative In vitro Cell Transformation Assay Hamster Negative In vitro Chromosome Aberration Hamster Positive In vitro Mammalian Cell Mutagenicity Mouse Lymphoma Positive In vitro Micronucleus Mouse Bone marrow Negative Carcinogenicity 2 years Rat Oral in feed 2000 mg/kg/day NOAEL Not carcinogenic 6 months Mouse Oral in feed 1000 mg/kg/day NOEL NJot carcinogenic Pfizer SDS</p> <p>Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m² basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan medoxomil.</p> <p>Both olmesartan medoxomil and olmesartan tested negative in the in vitro Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells in vitro (Chinese hamster lung) and both tested positive for thymidine kinase mutations in the in vitro mouse lymphoma assay. Olmesartan medoxomil tested negative in vivo for mutations in the MutaMouse intestine and kidney, and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested).</p> <p>Olmesartan medoxomil-hydrochlorothiazide in a ratio of 20:12.5 was negative in the Salmonella-Escherichia coli/mammalian microsome reverse mutation test up to the maximum recommended plate concentration for the standard assays. Olmesartan medoxomil and hydrochlorothiazide were tested individually and in combination ratios of 40:12.5, 20:12.5 and 10:12.5, for clastogenic activity in the in vitro Chinese hamster lung (CHL) chromosomal aberration assay. A positive response was seen for each component and combination ratio. However, no synergism in clastogenic activity was detected between olmesartan medoxomil and hydrochlorothiazide at any combination ratio.</p> <p>Olmesartan medoxomil-hydrochlorothiazide in a ratio of 20:12.5, administered orally, tested negative in the in vivo mouse bone marrow erythrocyte micronucleus assay at administered doses of up to 3144 mg/kg.</p> <p>Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.</p>
HYDROCHLOROTHIAZIDE	<p>Oral (woman) LDLo: 2.5 mg/kg/5d - I</p> <p>The following information refers to contact allergens as a group and may not be specific to this product.</p> <p>Contact allergies quickly manifest themselves as contact eczema, more rarely as urticaria or Quincke's oedema. The pathogenesis of contact eczema involves a cell-mediated (T lymphocytes) immune reaction of the delayed type. Other allergic skin reactions, e.g. contact urticaria, involve antibody-mediated immune reactions. The significance of the contact allergen is not simply determined by its sensitisation potential: the distribution of the substance and the opportunities for contact with it are equally important. A weakly sensitising substance which is widely distributed can be a more important allergen than one with stronger sensitising potential with which few individuals come into contact. From a clinical point of view, substances are noteworthy if they produce an allergic test reaction in more than 1% of the persons tested.</p> <p>Allergic reactions which develop in the respiratory passages as bronchial asthma or rhinoconjunctivitis, are mostly the result of reactions of the allergen with specific antibodies of the IgE class and belong in their reaction rates to the manifestation of the immediate type. In addition to the allergen-specific potential for causing respiratory sensitisation, the amount of the allergen, the exposure period and the genetically determined disposition of the exposed person are likely to be decisive. Factors which increase the sensitivity of the mucosa may play a role in predisposing a person to allergy. They may be genetically determined or acquired, for example, during infections or exposure to irritant substances. Immunologically the low molecular weight substances become complete allergens in the organism either by binding to peptides or proteins (haptens) or after metabolism (prohaptens).</p> <p>Particular attention is drawn to so-called atopic diathesis which is characterised by an increased susceptibility to allergic rhinitis, allergic bronchial asthma and atopic eczema (neurodermatitis) which is associated with increased IgE synthesis.</p> <p>Exogenous allergic alveolitis is induced essentially by allergen specific immune-complexes of the IgG type; cell-mediated reactions (T lymphocytes) may be involved. Such allergy is of the delayed type with onset up to four hours following exposure.</p> <p>WARNING: This substance has been classified by the IARC as Group 2B: Possibly Carcinogenic to Humans. NOTE: Substance has been shown to be mutagenic in at least one assay, or belongs to a family of chemicals producing damage or change to cellular DNA.</p>
AMLODIPINE BESYLATE	Olfaction effects, respiratory depression, ptosis, increased urine volume, reproductive effects, foetotoxicity, maternal effects recorded.
TALC	<p>No significant acute toxicological data identified in literature search.</p> <p>For talc (a form of magnesium silicate)</p> <p>The overuse of talc in nursing infants has resulted in pulmonary oedema, pneumonia and death within hours of inhaling talcum powder. The powder dries the mucous membranes of the bronchioles, disrupts pulmonary clearance, clogs smaller airways. Victims display wheezing, rapid or difficult breathing, increased pulse, cyanosis, fever. Mild exposure may cause relatively minor inflammatory lung disease. Long term exposure may show wheezing, weakness, productive cough, limited chest expansion, scattered rales, cyanosis.</p> <p>The substance is classified by IARC as Group 3: NOT classifiable as to its carcinogenicity to humans. Evidence of carcinogenicity may be inadequate or limited in animal testing.</p>
CELLULOSE & AMLODIPINE BESYLATE & TALC	Asthma-like symptoms may continue for months or even years after exposure to the material ends. This may be due to a non-allergic condition known as reactive airways dysfunction syndrome (RADS) which can occur after exposure to high levels of highly irritating

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compound. Main criteria for diagnosing RADS include the absence of previous airways disease in a non-atopic individual, with sudden onset of persistent asthma-like symptoms within minutes to hours of a documented exposure to the irritant. Other criteria for diagnosis of RADS include a reversible airflow pattern on lung function tests, moderate to severe bronchial hyperreactivity on methacholine challenge testing, and the lack of minimal lymphocytic inflammation, without eosinophilia. RADS (or asthma) following an irritating inhalation is an infrequent disorder with rates related to the concentration of and duration of exposure to the irritating substance. On the other hand, industrial bronchitis is a disorder that occurs as a result of exposure due to high concentrations of irritating substance (often particles) and is completely reversible after exposure ceases. The disorder is characterized by difficulty breathing, cough and mucus production.

Acute Toxicity	✓	Carcinogenicity	✗
Skin Irritation/Corrosion	✓	Reproductivity	✓
Serious Eye Damage/Irritation	✓	STOT - Single Exposure	✓
Respiratory or Skin sensitisation	✓	STOT - Repeated Exposure	✓
Mutagenicity	✓	Aspiration Hazard	✗

Legend: ✗ – Data either not available or does not fill the criteria for classification
 ✓ – Data available to make classification

SECTION 12 Ecological information

Toxicity

Ingredient	Endpoint	Test Duration (hr)	Species	Value	Source
Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide Tablets	Not Available	Not Available	Not Available	Not Available	Not Available
cellulose	Not Available	Not Available	Not Available	Not Available	Not Available
starch	Not Available	Not Available	Not Available	Not Available	Not Available
olmesartan medoxomil	LC50	96h	Fish	>10000mg/L	Not Available
hydrochlorothiazide	NOEC(ECx)	53h	Fish	0.012mg/L	4
amlodipine besylate	NOEC(ECx)	2h	Crustacea	0.5mg/l	4
talc	NOEC(ECx)	720h	Algae or other aquatic plants	918.089mg/l	2
	EC50	96h	Algae or other aquatic plants	7202.7mg/l	2
	LC50	96h	Fish	89581.016mg/l	2

Legend: *Extracted from 1. IUCLID Toxicity Data 2. Europe ECHA Registered Substances - Ecotoxicological Information - Aquatic Toxicity 4. US EPA, Ecotox database - Aquatic Toxicity Data 5. ECETOC Aquatic Hazard Assessment Data 6. NITE (Japan) - Bioconcentration Data 7. METI (Japan) - Bioconcentration Data 8. Vendor Data*

Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

DO NOT discharge into sewer or waterways.

Persistence and degradability

Ingredient	Persistence: Water/Soil	Persistence: Air
cellulose	LOW	LOW
hydrochlorothiazide	HIGH	HIGH

Bioaccumulative potential

Ingredient	Bioaccumulation
cellulose	LOW (LogKOW = -5.1249)
hydrochlorothiazide	LOW (LogKOW = -0.07)
amlodipine besylate	LOW (LogKOW = 2.12)

Mobility in soil

Ingredient	Mobility
cellulose	LOW (Log KOC = 10)
hydrochlorothiazide	LOW (Log KOC = 79.59)

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SECTION 13 Disposal considerations

Waste treatment methods

Product / Packaging disposal	<ul style="list-style-type: none"> ▶ Containers may still present a chemical hazard/ danger when empty. ▶ Return to supplier for reuse/ recycling if possible. <p>Otherwise:</p> <ul style="list-style-type: none"> ▶ If container can not be cleaned sufficiently well to ensure that residuals do not remain or if the container cannot be used to store the same product, then puncture containers, to prevent re-use, and bury at an authorised landfill. ▶ Where possible retain label warnings and SDS and observe all notices pertaining to the product. ▶ DO NOT allow wash water from cleaning or process equipment to enter drains. ▶ It may be necessary to collect all wash water for treatment before disposal. ▶ In all cases disposal to sewer may be subject to local laws and regulations and these should be considered first. ▶ Where in doubt contact the responsible authority.
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SECTION 14 Transport information

Labels Required

Marine Pollutant	NO
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Land transport (UN): NOT REGULATED FOR TRANSPORT OF DANGEROUS GOODS

Air transport (ICAO-IATA / DGR): NOT REGULATED FOR TRANSPORT OF DANGEROUS GOODS

Sea transport (IMDG-Code / GGVSee): NOT REGULATED FOR TRANSPORT OF DANGEROUS GOODS

14.7. Maritime transport in bulk according to IMO instruments

14.7.1. Transport in bulk according to Annex II of MARPOL and the IBC code

Not Applicable

14.7.2. Transport in bulk in accordance with MARPOL Annex V and the IMSBC Code

Product name	Group
cellulose	Not Applicable
starch	Not Applicable
olmesartan medoxomil	Not Applicable
hydrochlorothiazide	Not Applicable
amlodipine besylate	Not Applicable
talc	Not Applicable

14.7.3. Transport in bulk in accordance with the IGC Code

Product name	Ship Type
cellulose	Not Applicable
starch	Not Applicable
olmesartan medoxomil	Not Applicable
hydrochlorothiazide	Not Applicable
amlodipine besylate	Not Applicable
talc	Not Applicable

SECTION 15 Regulatory information

Safety, health and environmental regulations / legislation specific for the substance or mixture

cellulose is found on the following regulatory lists

International WHO List of Proposed Occupational Exposure Limit (OEL) Values for Manufactured Nanomaterials (MNMS)

starch is found on the following regulatory lists

Not Applicable

olmesartan medoxomil is found on the following regulatory lists

FEI Equine Prohibited Substances List - Banned Substances

FEI Equine Prohibited Substances List (EPSL)

hydrochlorothiazide is found on the following regulatory lists

FEI Equine Prohibited Substances List - Controlled Medication

FEI Equine Prohibited Substances List (EPSL)

International Agency for Research on Cancer (IARC) - Agents Classified by the IARC Monographs

International Agency for Research on Cancer (IARC) - Agents Classified by the IARC Monographs - Group 1: Carcinogenic to humans

amlodipine besylate is found on the following regulatory lists

Not Applicable

talc is found on the following regulatory lists

Chemical Footprint Project - Chemicals of High Concern List

International Agency for Research on Cancer (IARC) - Agents Classified by the IARC Monographs

International Agency for Research on Cancer (IARC) - Agents Classified by the IARC Monographs - Group 2A: Probably carcinogenic to humans

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International WHO List of Proposed Occupational Exposure Limit (OEL) Values for Manufactured Nanomaterials (MNMS)

Additional Regulatory Information

Not Applicable

National Inventory Status

National Inventory	Status
Australia - AIIC / Australia Non-Industrial Use	No (olmesartan medoxomil; amlodipine besylate)
Canada - DSL	No (olmesartan medoxomil; amlodipine besylate)
Canada - NDSL	No (olmesartan medoxomil; hydrochlorothiazide; amlodipine besylate; talc)
China - IECSC	No (olmesartan medoxomil; hydrochlorothiazide; amlodipine besylate)
Europe - EINEC / ELINCS / NLP	No (olmesartan medoxomil; amlodipine besylate)
Japan - ENCS	No (amlodipine besylate; talc)
Korea - KECI	No (olmesartan medoxomil; hydrochlorothiazide; amlodipine besylate)
New Zealand - NZIoC	No (olmesartan medoxomil)
Philippines - PICCS	No (olmesartan medoxomil; amlodipine besylate)
USA - TSCA	TSCA Inventory 'Active' substance(s) (cellulose; starch; hydrochlorothiazide; talc); No (olmesartan medoxomil; amlodipine besylate)
Taiwan - TCSI	Yes
Mexico - INSQ	No (olmesartan medoxomil; hydrochlorothiazide; amlodipine besylate)
Vietnam - NCI	No (olmesartan medoxomil)
Russia - FBEPH	No (olmesartan medoxomil; amlodipine besylate)
UAE - Control List (Banned/Restricted Substances)	No (cellulose; starch; olmesartan medoxomil; hydrochlorothiazide; amlodipine besylate; talc)
Legend:	Yes = All CAS declared ingredients are on the inventory No = One or more of the CAS listed ingredients are not on the inventory. These ingredients may be exempt or will require registration.

SECTION 16 Other information

Revision Date	31/10/2025
Initial Date	31/10/2025

SDS Version Summary

Version	Date of Update	Sections Updated
2.1	31/10/2025	Hazards identification - Classification, Composition / information on ingredients - Ingredients

Other information

Ingredients with multiple cas numbers

Name	CAS No
cellulose	9004-34-6, 68442-85-3, 1161712-52-2, 12656-52-9, 137261-76-8, 1374408-52-2, 152231-69-1, 1621420-37-8, 1873279-80-1, 189398-86-5, 209533-95-9, 2095812-59-0, 231290-83-8, 324745-49-5, 358787-62-9, 39394-43-9, 51395-76-7, 58968-67-5, 61991-21-7, 61991-22-8, 67016-75-5, 67016-76-6, 68073-05-2, 70225-79-5, 74623-16-8, 75398-83-3, 77907-70-1, 84503-75-3, 89468-66-6, 9006-02-4, 9012-19-5, 9037-50-7, 906542-14-1, 9076-30-6, 99331-82-5
starch	9005-25-8, 65996-63-6, 68441-21-4, 9005-84-9, 9057-07-2

Classification of the preparation and its individual components has drawn on official and authoritative sources as well as independent review by the Chemwatch Classification committee using available literature references.

The SDS is a Hazard Communication tool and should be used to assist in the Risk Assessment. Many factors determine whether the reported Hazards are Risks in the workplace or other settings. Risks may be determined by reference to Exposures Scenarios. Scale of use, frequency of use and current or available engineering controls must be considered.

Definitions and abbreviations

- ▶ PC - TWA: Permissible Concentration-Time Weighted Average
- ▶ PC - STEL: Permissible Concentration-Short Term Exposure Limit
- ▶ IARC: International Agency for Research on Cancer
- ▶ ACGIH: American Conference of Governmental Industrial Hygienists
- ▶ STEL: Short Term Exposure Limit
- ▶ TEEL: Temporary Emergency Exposure Limit,
- ▶ IDLH: Immediately Dangerous to Life or Health Concentrations
- ▶ ES: Exposure Standard
- ▶ OSF: Odour Safety Factor
- ▶ NOAEL: No Observed Adverse Effect Level
- ▶ LOAEL: Lowest Observed Adverse Effect Level
- ▶ TLV: Threshold Limit Value
- ▶ LOD: Limit Of Detection
- ▶ OTV: Odour Threshold Value
- ▶ BCF: BioConcentration Factors
- ▶ BEI: Biological Exposure Index
- ▶ DNEL: Derived No-Effect Level
- ▶ PNEC: Predicted no-effect concentration
- ▶ MARPOL: International Convention for the Prevention of Pollution from Ships
- ▶ IMSBC: International Maritime Solid Bulk Cargoes Code
- ▶ IGC: International Gas Carrier Code
- ▶ IBC: International Bulk Chemical Code

Continued...

Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide Tablets

- ▶ AIIC: Australian Inventory of Industrial Chemicals
- ▶ DSL: Domestic Substances List
- ▶ NDSL: Non-Domestic Substances List
- ▶ IECSC: Inventory of Existing Chemical Substance in China
- ▶ EINECS: European INventory of Existing Commercial chemical Substances
- ▶ ELINCS: European List of Notified Chemical Substances
- ▶ NLP: No-Longer Polymers
- ▶ ENCS: Existing and New Chemical Substances Inventory
- ▶ KECI: Korea Existing Chemicals Inventory
- ▶ NZIoC: New Zealand Inventory of Chemicals
- ▶ PICCS: Philippine Inventory of Chemicals and Chemical Substances
- ▶ TSCA: Toxic Substances Control Act
- ▶ TCSI: Taiwan Chemical Substance Inventory
- ▶ INSQ: Inventario Nacional de Sustancias Químicas
- ▶ NCI: National Chemical Inventory
- ▶ FBEPH: Russian Register of Potentially Hazardous Chemical and Biological Substances

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