SAFETY DATA SHEET

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

1.1. Product identifier

Trade name or designation of the mixture	VOLIBRIS TABLETS
Registration number	-
Synonyms	VOLIBRIS 5 MG TABLETS * VOLIBRIS 10 MG TABLETS * AMBRISENTAN, FORMULATED PRODUCT
Issue date	05-November-2014
Version number	02
Revision date	05-November-2014

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

Identified uses	Medicinal Product. This safety data sheet is written to provide health, safety and environmental information for people handling this formulated product in the workplace. It is not intended to provide information relevant to medicinal use of the product. In this instance patients should consult prescribing information/package insert/product label or consult their pharmacist or physician. For health and safety information for individual ingredients used during manufacturing, refer to the appropriate safety data sheet for each ingredient.
Uses advised against	No other uses are advised.

1.3. Details of the supplier of the safety data sheet

GlaxoSmithKline UK
980 Great West Road
Brentford, Middlesex TW8 9GS UK
UK General Information (normal business hours): +44-20-8047-5000
Email Address: msds@gsk.com
Website: www.gsk.com

1.4. Emergency telephone number

TRANSPORT EMERGENCIES::
UK In-country toll call: +(44)-870-8200418
International toll call: +1 703 527 3887
available 24 hrs/7 days; multi-language response

SECTION 2: Hazards identification

2.1. Classification of the substance or mixture

Classification according to Directive 67/548/EEC or 1999/45/EC as amended

Exempt from requirements - product regulated as a medicinal product, cosmetic product or medical device.

Classification according to Regulation (EC) No 1272/2008 as amended

Exempt from requirements - product regulated as a medicinal product, cosmetic product or medical device.

2.2. Label elements

Label according to Regulation (EC) No. 1272/2008 as amended

Exempt from requirements - product regulated as a medicinal product, cosmetic product or medical device.

2.3. Other hazards Caution - Pharmaceutical agent. See section 11 for additional information on health hazards.

SECTION 3: Composition/information on ingredients

3.2. Mixtures

General information

Chemical name	%	CAS-No. / EC No.	REACH Registration No.	INDEX No.	Notes
MICROCRYSTALLINE CELLULOSE	< 25	9004-34-6 232-674-9	-	-	
Classification: **DSD:** -					
CLP: -					
AMBRISENTAN	3.4 - < 7	177036-94-1 -	-	-	
Classification: **DSD:** Repr. Cat. 2;R60-61					
CLP: Repr. 1B;H360FD					
MAGNESIUM STEARATE	< 1	557-04-0 209-150-3	-	-	
Classification: **DSD:** -					
CLP: -					
Talc	< 1	14807-96-6 238-877-9	-	-	
Classification: **DSD:** -					
CLP: -					
Titanium dioxide	< 1	13463-67-7 236-675-5	-	-	
Classification: **DSD:** -					
CLP: -					

Other components below reportable levels 60 - < 70

List of abbreviations and symbols that may be used above

CLP: Regulation No. 1272/2008.
DSD: Directive 67/548/EEC.
M: M-factor
vPvB: very persistent and very bioaccumulative substance.
PBT: persistent, bioaccumulative and toxic substance.
#: This substance has been assigned Community workplace exposure limit(s).

SECTION 4: First aid measures

General information In the case of accident or if you feel unwell, seek medical advice immediately (show the label where possible). Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves.

4.1. Description of first aid measures

Inhalation Move to fresh air. If breathing is difficult, trained personnel should give oxygen. Call a physician if symptoms develop or persist. Under normal conditions of intended use, this material is not expected to be an inhalation hazard.

Skin contact Immediately flush skin with plenty of water. Take off contaminated clothing and wash before reuse. Get medical attention if symptoms occur.

Eye contact Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician.

Ingestion If swallowed, rinse mouth with water (only if the person is conscious). If ingestion of a large amount does occur, call a poison control centre immediately. Do not induce vomiting without advice from poison control center.

4.2. Most important symptoms and effects, both acute and delayed None known.
The following adverse effects have been noted with therapeutic use of this material: headache; flushing; dizziness.

4.3. Indication of any immediate medical attention and special treatment needed No specific antidotes are recommended. Treat according to locally accepted protocols. For additional guidance, refer to the current prescribing information or to the local poison control information centre.

SECTION 5: Firefighting measures

General fire hazards No unusual fire or explosion hazards noted.

5.1. Extinguishing media

Suitable extinguishing media	Water. Foam. Dry chemical powder. Carbon dioxide (CO2).
Unsuitable extinguishing media	None known.
5.2. Special hazards arising from the substance or mixture	During fire, gases hazardous to health may be formed.

5.3. Advice for firefighters

Special protective equipment for firefighters	Self-contained breathing apparatus and full protective clothing must be worn in case of fire.
Special fire fighting procedures	Move containers from fire area if you can do so without risk.
Specific methods	Use standard firefighting procedures and consider the hazards of other involved materials.

SECTION 6: Accidental release measures

6.1. Personal precautions, protective equipment and emergency procedures

For non-emergency personnel	Keep unnecessary personnel away. Keep people away from and upwind of spill/leak. Keep out of low areas. Do not touch damaged containers or spilled material unless wearing appropriate protective clothing. For personal protection, see section 8.
For emergency responders	Keep unnecessary personnel away. Use personal protection recommended in Section 8 of the SDS.
6.2. Environmental precautions	Avoid discharge into drains, water courses or onto the ground.
6.3. Methods and material for containment and cleaning up	Stop the flow of material, if this is without risk. Prevent entry into waterways, sewer, basements or confined areas. Following product recovery, flush area with water.
6.4. Reference to other sections	For personal protection, see section 8. For waste disposal, see section 13 of the SDS.

SECTION 7: Handling and storage

7.1. Precautions for safe handling	Avoid prolonged exposure. Observe good industrial hygiene practices.
7.2. Conditions for safe storage, including any incompatibilities	Store in original tightly closed container. Store away from incompatible materials (see Section 10 of the SDS).
7.3. Specific end use(s)	Medicinal Product.

SECTION 8: Exposure controls/personal protection

8.1. Control parameters

Occupational exposure limits

GSK

Components	Type	Value	Note
AMBRISENTAN (CAS 177036-94-1)	8 HR TWA	20 mcg/m3	
	OHC	3	Reproductive hazard
MICROCRYSTALLINE CELLULOSE (CAS 9004-34-6)	OHC	1	

Ireland. Occupational Exposure Limits

Components	Type	Value	Form
MAGNESIUM STEARATE (CAS 557-04-0)	TWA	10 mg/m3	
MICROCRYSTALLINE CELLULOSE (CAS 9004-34-6)	STEL	20 mg/m3	Total inhalable dust.
	TWA	4 mg/m3	Respirable dust.
		10 mg/m3	Total inhalable dust.
Talc (CAS 14807-96-6)	TWA	10 mg/m3	Total inhalable dust.
		0.8 mg/m3	Respirable dust.
Titanium dioxide (CAS 13463-67-7)	TWA	4 mg/m3	Respirable dust.
		10 mg/m3	Total inhalable dust.

Biological limit values	No biological exposure limits noted for the ingredient(s).
Recommended monitoring procedures	Follow standard monitoring procedures.

Derived no-effect level (DNEL)	Not available.
Predicted no effect concentrations (PNECs)	Not available.

Exposure guidelines

8.2. Exposure controls

Appropriate engineering controls	General ventilation normally adequate.

Individual protection measures, such as personal protective equipment

General information	Personal protection equipment should be chosen according to the CEN standards and in discussion with the supplier of the personal protective equipment. Follow all local regulations if personal protective equipment (PPE) is used in the workplace.
Eye/face protection	Not normally needed. If contact is likely, safety glasses with side shields are recommended. (e.g. EN 166).
Skin protection	
- Hand protection	Not normally needed. For prolonged or repeated skin contact use suitable protective gloves. Select suitable chemical resistant protective gloves (EN 374) with a protective index 6 (>480min permeation time).
- Other	Not normally needed. Wear suitable protective clothing as protection against splashing or contamination. (EN 14605 for splashes, EN ISO 13982 for dust).
Respiratory protection	No personal respiratory protective equipment normally required. When workers are facing concentrations above the exposure limit they must use appropriate certified respirators. Where breathable aerosols/dust are formed, use suitable combination filter for gases/vapours of organic, inorganic, acid inorganic, alkaline compounds and toxic particles (eg. EN 14387).
Thermal hazards	Wear appropriate thermal protective clothing, when necessary.
Hygiene measures	Always observe good personal hygiene measures, such as washing after handling the material and before eating, drinking, and/or smoking. Routinely wash work clothing and protective equipment to remove contaminants. For advice on suitable monitoring methods, seek guidance from a qualified environment, health and safety professional. New or expectant mothers might be at greater risk from overexposure. Risk assessments must take this into consideration. Female employees anticipating pregnancy or with a confirmed pregnancy must be encouraged to notify an occupational health professional or their line manager. This will act as the trigger for individual re-assessment of the employee's work practices.

Environmental exposure controls

Hazard guidance and control recommendations	Environmental manager must be informed of all major releases.

SECTION 9: Physical and chemical properties

9.1. Information on basic physical and chemical properties

Appearance

Physical state	Solid.
Form	Tablet.
Colour	Not available.
Odour	Not available.
Odour threshold	Not available.
pH	Not available.
Melting point/freezing point	Not available.
Initial boiling point and boiling range	Not available.
Flash point	Not available.
Evaporation rate	Not available.
Flammability (solid, gas)	Not available.

Upper/lower flammability or explosive limits

Flammability limit - lower (%)	Not available.
Flammability limit - upper (%)	Not available.
Vapour pressure	Not available.
Vapour density	Not available.
Relative density	Not available.

Solubility(ies)

Solubility (water)	Not available.
Solubility (other)	Not available.
Partition coefficient (n-octanol/water)	Not available.
Auto-ignition temperature	Not available.
Decomposition temperature	Not available.
Viscosity	Not available.
Explosive properties	Not available.
Oxidizing properties	Not available.
9.2. Other information	No relevant additional information available.

SECTION 10: Stability and reactivity

10.1. Reactivity	The product is stable and non-reactive under normal conditions of use, storage and transport.
10.2. Chemical stability	Material is stable under normal conditions.
10.3. Possibility of hazardous reactions	No dangerous reaction known under conditions of normal use.
10.4. Conditions to avoid	Contact with incompatible materials.
10.5. Incompatible materials	Strong oxidising agents. Fluorine.
10.6. Hazardous decomposition products	None known. Irritating and/or toxic fumes and gases may be emitted upon the product's decomposition.

SECTION 11: Toxicological information

General information	Occupational exposure to the substance or mixture may cause adverse effects.

Information on likely routes of exposure

Inhalation	Under normal conditions of intended use, this material is not expected to be an inhalation hazard.
Skin contact	Health injuries are not known or expected under normal use. Dust or powder may irritate the skin.
Eye contact	Health injuries are not known or expected under normal use. Dust or powder may irritate eye tissue.
Ingestion	Health injuries are not known or expected under normal use. May be harmful if swallowed. However, ingestion is not likely to be a primary route of occupational exposure.
Symptoms	None known. The following adverse effects have been noted with therapeutic use of this material: headache; flushing; dizziness.

11.1. Information on toxicological effects

Acute toxicity Health injuries are not known or expected under normal use. May be harmful if swallowed.

Components	Species	Test results
AMBRISENTAN (CAS 177036-94-1)		
Acute		
Oral		
LD50	Rat	>= 3160 mg/kg
MAGNESIUM STEARATE (CAS 557-04-0)		
Acute		
Oral		
LD50	Rat	> 2000 mg/kg
MICROCRYSTALLINE CELLULOSE (CAS 9004-34-6)		
Acute		
Dermal		
LD50	Rabbit	> 2000 mg/kg
Oral		
LD50	Rat	> 2000 mg/kg
Titanium dioxide (CAS 13463-67-7)		
Acute		
Inhalation		
LC50	Rat	6820 mcg/m3

Components	Species	Test results
Oral		
LD50	Rat	> 24 g/kg
Chronic		
Inhalation		
LOEC	Rat	8.6 mg/m3, 1 years TiO2 accumulated in interstitial macrophages, aggregated interstitial cells and particle laden macrophrages in lymphoid tissue.
NOAEC	Rat	250 mg/m3, 2 years Highest dose
		5 mg/m3, 24 months
Subacute		
Inhalation		
LOEL	Rat	0.1 - 35 mg/m3, 4 weeks Mild macrophage hyperplasia, no change in bronchio-alveolar lavage fluid.
NOAEC	Guinea pig	26 mg/m3, 3 weeks No evidence of significant inflammation in respiratory tract.
Oral		
NOAEL	Rat	100000 ppm, 14 Day Dietary study, highest dose tested.
Subchronic		
Inhalation		
LOEC	Rat	3.2 - 20 mg/m3, 8 min Accumulation of TiO2 in macrophages and evidence of pulmonary inflammation.

* Estimates for product may be based on additional component data not shown.

Skin corrosion/irritation Health injuries are not known or expected under normal use.

Irritation Corrosion - Skin

TITANIUM DIOXIDE	0, Literature data Result: Non-irritant Species: Guinea pig 0, Literature data Result: Non-irritant Species: Human Acute dermal irritation; OECD 404, Literature data Result: Non-irritant Species: Rabbit
AMBRISENTAN	Reconstituted Human Epidermis (RHE) Result: Negative - Not likely to be a significant irritant.

Irritation Corrosion - Skin: P.I.I. value

MAGNESIUM STEARATE	0

Serious eye damage/eye irritation Health injuries are not known or expected under normal use. Dust or powder may irritate eye tissue.

Eye

TITANIUM DIOXIDE	OECD 405, Literature data Result: Mild irritant Species: Rabbit
AMBRISENTAN	Reconstituted Human Corneal Epithelium (HCE) Result: Negative; not likely to be a severe irritant

Eye / Kay and Calandra class - Intact

MAGNESIUM STEARATE	4 Recovery Period: 2 days

Respiratory sensitisation Not available.

Skin sensitisation Health injuries are not known or expected under normal use.

Sensitisation

TITANIUM DIOXIDE	5 % Optimisation Test, Literature data - Vehicle: petrolatum Result: negative Species: Guinea pig Test Duration: 48 hour exposure
AMBRISENTAN	OECD 429 / Local Lymph Node Assay, Maximum concentration = 50%; vehicle = DMF Result: negative Species: Mouse

Sensitisation

TITANIUM DIOXIDE	Patch test, Literature data Result: negative Species: Human

Germ cell mutagenicity Health injuries are not known or expected under normal use.

Mutagenicity

AMBRISENTAN	Ames Assay, GLP assay Result: negative
TITANIUM DIOXIDE	Ames, Literature data Result: negative
AMBRISENTAN	Chromosomal Aberration Assay In Vitro Result: positive
TITANIUM DIOXIDE	Micronucleus Assay in vitro, CHO cells, Literature data Result: negative
	Micronucleus Assay in vitro, cultured human peripheral lymphocytes, Literature data Result: positive
AMBRISENTAN	Micronucleus Assay, GLP assay Result: negative Species: Rat
TITANIUM DIOXIDE	Syrian Hamster Embryo (SHE) cell transformation assay Result: negative
AMBRISENTAN	Unscheduled DNA Synthesis in vivo Result: negative Species: Rat
TITANIUM DIOXIDE	WIL2-NS HPRT/ t-Thioguanidine - Human B-Cell lymphoblastoid, Literature data Result: positive

Carcinogenicity Health injuries are not known or expected under normal use. Contains a material (titanium dioxide) classified as a carcinogen by external agencies. Carcinogenic activity was seen in inhalation studies using laboratory animals. High concentrations or doses administered over an extended period of time were required to produce adverse effects.

TITANIUM DIOXIDE	0.5 mg/m3, Literature data Result: negative Species: Rat Test Duration: 24 months 0.72 - 14.8 mg/m3, Literature data Result: negative Species: Mouse 10 - 250 mg/m3, Dietary study - Literature data. Result: Inflammation at all doses with alveolar/bronchiolar adenoma at the highest concentration. Species: Rat Test Duration: 24 months 25000 - 50000 ppm, Dietary study Result: negative Species: Mouse 25000 - 50000 ppm, Dietary study - Literature data. Result: negative Species: Rat 7.2 - 14.8 mg/m3, Literature data Result: Lung tumour Species: Rat Test Duration: 24 months

IARC Monographs. Overall Evaluation of Carcinogenicity

Titanium dioxide (CAS 13463-67-7)	2B Possibly carcinogenic to humans.

Reproductive toxicity Suspected of damaging fertility or the unborn child.

Reproductivity

AMBRISENTAN	Embryo-foetal development Result: Foetal toxicity, malformations in multiple species; endothelin receptor antagonist class effect Fertility, Male Result: Testicular toxicity, reduced fertility in mice and rats

Specific target organ toxicity - single exposure None known.

Specific target organ toxicity - repeated exposure None known.

Aspiration hazard Not available.

Mixture versus substance information	No information available.
Other information	Caution - Pharmaceutical agent. Occupational exposure to the substance or mixture may cause adverse effects.

SECTION 12: Ecological information

12.1. Toxicity Not expected to be harmful to aquatic organisms.

Components		Species	Test results
AMBRISENTAN (CAS 177036-94-1)			
Aquatic			
Acute			
Algae	EC50	Algae	10 - 100 mg/l, 96 hours QSAR Estimate
Crustacea	EC50	Daphnia	10 - 100 mg/l, 48 hours QSAR Estimate
Fish	EC50	Fish	10 - 100 mg/l, 96 hours QSAR Estimate
MAGNESIUM STEARATE (CAS 557-04-0)			
Aquatic			
Acute			
Fish	EC50	Orange-red killfish (Adult Oryzias latipes)	130 mg/l, 96 hours
Talc (CAS 14807-96-6)			
Aquatic			
Acute			
Fish	EC50	Zebra fish (Adult Brachydanio rerio)	> 100 g/l, 24 hours Static renewal test
Titanium dioxide (CAS 13463-67-7)			
Aquatic			
Acute			
Crustacea	EC50	Water flea (Daphnia magna)	> 1000 mg/l, 48 hours Static test

* Estimates for product may be based on additional component data not shown.

12.2. Persistence and degradability

Photolysis

Half-life (Photolysis-atmospheric)

MAGNESIUM STEARATE 17 Hours Estimated

UV/visible spectrum wavelength

MAGNESIUM STEARATE 210 nm

Biodegradability

Percent degradation (Aerobic biodegradation-inherent)

MAGNESIUM STEARATE 77 %, 28 days BOD

Percent degradation (Aerobic biodegradation-ready)

MAGNESIUM STEARATE 95 %, 22 days Sturm test

Percent degradation (Aerobic biodegradation-soil)

MAGNESIUM STEARATE 50 %, 13 days

12.3. Bioaccumulative potential

Partition coefficient n-octanol/water (log Kow)

AMBRISENTAN 1.2 (Measured).

Bioconcentration factor (BCF)

MAGNESIUM STEARATE > 9999 Estimated

12.4. Mobility in soil

Adsorption

Soil/sediment sorption - log Koc

MAGNESIUM STEARATE 5.86 Estimated

Mobility in general	Not available.
12.5. Results of PBT and vPvB assessment	Not available.
12.6. Other adverse effects	Not available.

SECTION 13: Disposal considerations

13.1. Waste treatment methods

Residual waste	Dispose of in accordance with local regulations. Empty containers or liners may retain some product residues. This material and its container must be disposed of in a safe manner (see: Disposal instructions). Avoid discharge into water courses or onto the ground.
Contaminated packaging	Empty containers should be taken to an approved waste handling site for recycling or disposal. Since emptied containers may retain product residue, follow label warnings even after container is emptied.
EU waste code	The Waste code should be assigned in discussion between the user, the producer and the waste disposal company.
Disposal methods/information	Collect and reclaim or dispose in sealed containers at licensed waste disposal site. Do not discharge into drains, water courses or onto the ground. Dispose in accordance with all applicable regulations.
Special precautions	Dispose in accordance with all applicable regulations.

SECTION 14: Transport information

ADR

Not regulated as dangerous goods.

RID

Not regulated as dangerous goods.

ADN

Not regulated as dangerous goods.

IATA

Not regulated as dangerous goods.

IMDG

Not regulated as dangerous goods.

14.7. Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	MARPOL Annex II applies to liquids used in a ship's operation that pose a threat to the marine environment. These materials may not be transported in bulk.

SECTION 15: Regulatory information

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

EU regulations

Regulation (EC) No. 1005/2009 on substances that deplete the ozone layer, Annex I

Not listed.

Regulation (EC) No. 1005/2009 on substances that deplete the ozone layer, Annex II

Not listed.

Regulation (EC) No. 850/2004 On persistent organic pollutants, Annex I as amended

Not listed.

Regulation (EC) No. 689/2008 concerning the export and import of dangerous chemicals, Annex I, part 1 as amended

Not listed.

Regulation (EC) No. 689/2008 concerning the export and import of dangerous chemicals, Annex I, part 2 as amended

Not listed.

Regulation (EC) No. 689/2008 concerning the export and import of dangerous chemicals, Annex I, part 3 as amended

Not listed.

Regulation (EC) No. 689/2008 concerning the export and import of dangerous chemicals, Annex V as amended

Not listed.

Regulation (EC) No. 166/2006 Annex II Pollutant Release and Transfer Registry

Not listed.

Regulation (EC) No. 1907/2006, REACH Article 59(10) Candidate List as currently published by ECHA

Not listed.

Authorisations

Regulation (EC) No. 1907/2006, REACH Annex XIV Substances subject to authorization, as amended

Not listed.

Restrictions on use

Regulation (EC) No. 1907/2006, REACH Annex XVII Substances subject to restriction on marketing and use as amended

Not listed.

Directive 2004/37/EC: on the protection of workers from the risks related to exposure to carcinogens and mutagens at work

Not listed.

Directive 92/85/EEC: on the safety and health of pregnant workers and workers who have recently given birth or are breastfeeding

Not listed.

Other EU regulations

Directive 96/82/EC (Seveso II) on the control of major-accident hazards involving dangerous substances

Not listed.

Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work

Not listed.

Directive 94/33/EC on the protection of young people at work

Not listed.

Other regulations	The product is classified and labelled in accordance with EC directives or respective national laws. This Safety Data Sheet complies with the requirements of Regulation (EC) No 1907/2006.
National regulations	Follow national regulation for work with chemical agents.
15.2. Chemical safety assessment	No Chemical Safety Assessment has been carried out.

SECTION 16: Other information

List of abbreviations	Not available.
References	GSK Hazard Determination
Information on evaluation method leading to the classification of mixture	The classification for health and environmental hazards is derived by a combination of calculation methods and test data, if available.
Full text of any statements or R-phrases and H-statements under Sections 2 to 15	R60 May impair fertility. R61 May cause harm to the unborn child. H360FD May damage fertility. May damage the unborn child.
Revision information	Product and Company Identification: Product and Company Identification Composition / Information on Ingredients: Ingredients Exposure Controls / Personal Protection: Physical & Chemical Properties: Regulatory Information: United States GHS: Classification
Training information	Follow training instructions when handling this material.
Disclaimer	The information and recommendations in this safety data sheet are, to the best of our knowledge, accurate as of the date of issue. Nothing herein shall be deemed to create any warranty, express or implied. It is the responsibility of the user to determine the applicability of this information and the suitability of the material or product for any particular purpose.