

Drug Regulatory Affairs

Foradil[®] Aerolizer[®]
(formoterol fumarate inhalation powder) 12 mcg

Pulmonary-Allergy Drugs Advisory Committee on the safety of
long-acting beta-agonist bronchodilators

NDA 20-831

Appendix 1 – List of pre-defined terms

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1 Introduction

The Formoterol Clinical Safety Database contains demographic and safety data loaded from individual clinical trial databases for all centrally planned studies in the Foradil program. In order to pool data in this database, variables from the trial databases have been mapped and transcribed into a common format to enable integration of data for summaries from a variety of subsets of trials. As the trials have been conducted over a period of more than 15 years, it has been necessary to make certain changes especially concerning the dictionaries used to encode data concerning adverse events and concomitant medications. Any such changes have been fully documented and applied as programmed algorithms which are validated and archived according to Novartis internal procedures.

2 Subsets of trials

A number of subsets of asthma trials carried out using formoterol delivered by the Aerolizer and Certihaler® devices have been used for the investigation of safety for this Briefing Book. For each in-text table the appropriate subset of trials used has been described.

The subsets used are as follows:

- all controlled trials irrespective of length of exposure;
- all uncontrolled trials irrespective of length of exposure;
- multiple-dose controlled trials over at least 4 weeks duration;
- multiple-dose placebo-controlled trials over at least 4 weeks duration;
- multiple-dose placebo-controlled trials over at least 4 weeks duration excluding cross-over trials.

Summary tables have been produced based on these subsets for Aerolizer plus Certihaler and for Aerolizer trials alone by treatment and by dose.

In addition, similar tables have been prepared for the COPD indication, although no uncontrolled trials in COPD have been carried out and all multiple dose controlled trials included a placebo control.

The studies included are as follows:

Table 1 **Multiple dose controlled trials
of at least 4 weeks duration**

Asthma		COPD
Aerolizer	Certihaler	Aerolizer
D2307	F604	D2308
DPPD2	F605	PROT56
DPPD5	F2302	PROT58
DPRD1	F2303	
DPRD2		
DPRD3		
FOOD1		
FORINT02		
FOS02		
FOSA1		
FOUK2		
MTA03		
MXF1		
PROT40		
PROT41		
PROT49		
PROT62		
PROT73		

Table 2 Multiple dose controlled trials
of less than 4 weeks duration
and single dose trials

Asthma		COPD
Aerolizer	Certihaler	Aerolizer
DPDA2	F601	FOR-INT-03
DPDF0	F602	
DPDF1		
DPDF2		
DPDF3		
DPDF4		
DPEX1		
DPFL2		
DPME1		
DPME2		
DPNA1		
DPNA2		
DPON1		
DPON2		
DPPD1		
DPPD3		
DPPD6		
DPPK1		
DPSP2		
DPSP4		
FOIT2		
FORS02		
MTA02		
PROT45		
PROT46		
PROT54		

Table 3 Multiple dose uncontrolled trials

Asthma	
Aerolizer	Certihaler
DPPD2F	F603
DPRD1F	
DPRD2F	
DPRD3F	
FFOR14	

3 Definitions used in tables

Lists of MedDRA preferred terms were prepared to predefine subgroups of events as ‘asthma-related’, ‘COPD-related’ and ‘cardiovascular’. These definitions are included below.

Asthma-related

asthma, dyspnea, bronchospasm, chest discomfort, cough, wheezing, dyspnea exacerbated, status asthmaticus, respiratory distress, acute respiratory failure, hypoxia

COPD-related

chronic obstructive pulmonary disease, chronic obstructive airway disease exacerbated, cough (excluding cough decreased), any term containing ‘dyspnea’, lower respiratory tract infection, chronic bronchitis, bronchospasm, bronchial obstruction, respiratory failure

Cardiovascular

all cardiac system organ class, all vascular system organ class except ‘flushing’, ‘haematoma’, ‘hot flush’, ‘pallor’, ‘lymphagitis’, general system organ class includes ‘cardiac death’, ‘oedema due to cardiac disease’, ‘sudden cardiac death’, nervous system organ class includes ‘anterior spinal’, ‘artery syndrome’, ‘basilar artery occlusion’, ‘basilar artery stenosis’, ‘basilar artery thrombosis’, ‘brain stem haemorrhage’, ‘brain stem infarction’, ‘brain stem ischaemia’, ‘brain stem thrombosis’, ‘carotid aneurysm rupture’, ‘carotid arterial embolus’, ‘carotid artery aneurysm’, ‘carotid artery atheroma’, ‘carotid artery disease’, ‘carotid artery dissection’, ‘carotid artery occlusion’, ‘carotid artery stenosis’, ‘carotid artery thrombosis’, ‘cerebellar artery occlusion’, ‘cerebellar artery thrombosis’, ‘cerebellar haematoma’, ‘cerebellar haemorrhage’, ‘cerebellar infarction’, ‘cerebral artery embolism’, ‘cerebral artery occlusion’, ‘cerebral artery stenosis’, ‘cerebral artery thrombosis’, ‘cerebral atherosclerosis’, ‘cerebral circulatory failure’, ‘cerebral haematoma’, ‘cerebral haemorrhage’, ‘cerebral haemorrhage foetal’, ‘cerebral haemorrhage neonatal’, ‘cerebral infarction’, ‘cerebral infarction foetal’, ‘cerebral ischaemia’, ‘cerebral thrombosis’, ‘cerebral venous thrombosis’, ‘cerebrospinal thrombotic tamponade’, ‘cerebrovascular accident’, ‘cerebrovascular disorder’, ‘cerebrovascular insufficiency’, ‘cerebrovascular spasm’, ‘cerebrovascular stenosis’, ‘charcot-bouchard microaneurysms’, ‘embolic cerebral infarction’, ‘embolic stroke’, ‘foetal cerebrovascular disorder’, ‘haemorrhage intracranial’, ‘haemorrhagic cerebral infarction’, ‘haemorrhagic stroke’, ‘haemorrhagic transformation stroke’, ‘hypertensive encephalopathy’, ‘intracranial aneurysm’, ‘intracranial haematoma’, ‘intracranial venous sinus thrombosis’, ‘intraventricular haemorrhage’, ‘intraventricular haemorrhage neonatal’, ‘ischaemic cerebral infarction’, ‘ischaemic neuropathy’, ‘ischaemic stroke’, ‘lacunar infarction’, ‘precerebral artery occlusion’, ‘putamen haemorrhage’, ‘reversible ischaemic neurological deficit’, ‘ruptured cerebral aneurysm’, ‘spinal artery embolism’, ‘spinal cord haemorrhage’, ‘spinal cord infarction’, ‘spinal cord ischaemia’, ‘spinal epidural haemorrhage’, ‘spinal haematoma’, ‘spinal vascular disorder’, ‘stroke in evolution’, ‘subarachnoid haemorrhage’, ‘subarachnoid haemorrhage neonatal’, ‘subdural haemorrhage neonatal’, ‘superior sagittal sinus thrombosis’, ‘thalamus haemorrhage’, ‘thromboembolic stroke’, ‘thrombotic stroke’, ‘transient ischaemic attack’, ‘transverse sinus thrombosis’, ‘vertebral artery occlusion’, ‘vertebral artery stenosis’, ‘vertebral artery thrombosis’, ‘vertebrobasilar insufficiency’,

investigations system organ class includes 'arteriogram carotid abnormal', 'arteriogram coronary abnormal', 'atrial natriuretic peptide abnormal', 'atrial natriuretic peptide increased', 'atrial pressure increased', 'biopsy heart abnormal', 'biopsy pericardium abnormal', 'blood creatine phosphokinase mb abnormal', 'blood creatine phosphokinase mb increased', 'blood pressure abnormal', 'blood pressure ambulatory abnormal', 'blood pressure ambulatory decreased', 'blood pressure ambulatory increased', 'blood pressure decreased', 'blood pressure diastolic abnormal', 'blood pressure diastolic decreased', 'blood pressure diastolic increased', 'blood pressure increased', 'blood pressure orthostatic abnormal', 'blood pressure orthostatic decreased', 'blood pressure orthostatic increased', 'blood pressure systolic abnormal', 'blood pressure systolic decreased', 'blood pressure systolic increased', 'blood pressure systolic inspiratory decreased', 'brain natriuretic peptide abnormal', 'brain natriuretic peptide increased', 'cardiac electrophysiologic study abnormal', 'cardiac enzymes increased', 'cardiac function test abnormal', 'cardiac imaging procedure abnormal', 'cardiac index abnormal', 'cardiac index decreased', 'cardiac index increased', 'cardiac monitoring abnormal', 'cardiac murmur', 'cardiac murmur functional', 'cardiac output decreased', 'cardiac output increased', 'cardiac stress test abnormal', 'cardiac telemetry abnormal', 'cardiac ventriculogram abnormal', 'cardiac ventriculogram left abnormal', 'cardiac ventriculogram right abnormal', 'cardiovascular autonomic function test abnormal', 'cardiovascular function test abnormal', 'central venous pressure abnormal', 'central venous pressure decreased', 'central venous pressure increased', 'decreased ventricular afterload', 'decreased ventricular preload', 'ECG p wave inverted', 'ECG signs of myocardial ischaemia', 'ECG signs of ventricular hypertrophy', 'echocardiogram abnormal', 'ejection fraction abnormal', 'ejection fraction decreased', 'electrocardiogram p pulmonale', 'electrocardiogram p wave abnormal', 'electrocardiogram p wave biphasic', 'electrocardiogram pq interval prolonged', 'electrocardiogram pr prolongation', 'electrocardiogram pr shortened', 'electrocardiogram q wave abnormal', 'electrocardiogram qrs complex abnormal', 'electrocardiogram qrs complex prolonged', 'electrocardiogram qrs complex shortened', 'electrocardiogram qt corrected interval prolonged', 'electrocardiogram qt corrected interval shortened', 'electrocardiogram qt interval abnormal', 'electrocardiogram qt prolonged', 'electrocardiogram qt shortened', 'electrocardiogram r on t phenomenon', 'electrocardiogram st segment abnormal', 'electrocardiogram st segment depression', 'electrocardiogram st segment elevation', 'electrocardiogram st-t change', 'electrocardiogram st-t segment abnormal', 'electrocardiogram st-t segment depression', 'electrocardiogram st-t segment elevation', 'electrocardiogram t wave abnormal', 'electrocardiogram t wave amplitude decreased', 'electrocardiogram t wave amplitude increased', 'electrocardiogram t wave biphasic', 'electrocardiogram t wave inversion', 'electrocardiogram t wave peaked', 'electrocardiogram u wave inversion', 'electrocardiogram u-wave abnormality', 'electrocardiogram u-wave biphasic', 'electrocardiogram abnormal', 'electrocardiogram ambulatory abnormal', 'electrocardiogram change', 'electrocardiogram delta waves abnormal', 'electrocardiogram low voltage', 'electrocardiogram poor r-wave progression', 'electrocardiogram repolarisation abnormality', 'exercise electrocardiogram abnormal', 'heart rate abnormal', 'heart rate decreased', 'heart rate increased', 'heart rate irregular', 'heart sounds abnormal', 'increased ventricular afterload', 'increased ventricular preload', 'left ventricular end-diastolic pressure decreased', 'left ventricular end-diastolic pressure increased', 'mean arterial pressure decreased', 'mean arterial pressure increased', 'pulmonary arterial pressure abnormal', 'pulmonary arterial pressure decreased', 'pulmonary arterial pressure increased', 'pulmonary arterial wedge pressure abnormal', 'pulmonary arterial wedge pressure decreased',

'pulmonary arterial wedge pressure increased', 'pulse abnormal', 'pulse absent', 'pulse pressure abnormal', 'pulse pressure decreased', 'pulse pressure increased', 'pulse waveform abnormal', 'qrs axis abnormal', 'right ventricular systolic pressure decreased', 'right ventricular systolic pressure increased', 'scan myocardial perfusion abnormal', 'stroke volume decreased', 'stroke volume increased', 'troponin i increased', 'troponin t increased', 'troponin increased', 'vascular resistance pulmonary decreased', 'vascular resistance systemic decreased', 'vascular resistance systemic increased', 'venous pressure abnormal', 'venous pressure decreased', 'venous pressure increased', 'venous pressure jugular abnormal', 'venous pressure jugular decreased', 'venous pressure jugular increased', 'ventricular internal diameter abnormal'

4 Coding of deaths

Subsequent to locking the database for this report, a review of SAE narratives for deaths which occurred in the clinical trials resulted in the reclassification of two cases as being asthma-related (these cases had not previously been identified as asthma-related using the predefined terms described in Section 3 of this Appendix), and the addition of one additional asthma-related death. These three patients, described below, have been included in Table 3-3 of the Briefing Book as having experienced asthma-related deaths.

1. F603: One patient's reported cause of death of "respiratory arrest" was reclassified in Table 3-3 as asthma-related (SAE narrative indicates the patient's respiratory arrest was due to an asthma attack)
2. Protocol 41: One patient's reported cause of death of "cardiac and respiratory arrest" was reclassified in Table 3-3 as asthma-related instead of cardiovascular (SAE narrative indicates respiratory arrest was the precipitating event for the cardiac arrest, and on the death certificate the cause of death was "status asthmaticus")
3. FFOR14: One patient was added to Table 3-3 as an asthma-related death. (SAE narrative indicates that dates of study drug treatment were 16 Aug to 8 Sept 95, with the date of onset of the SAE [status asthmaticus] 7 Sept 95, and the date of death 9 Sept 95).