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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

Mysimba

combination of INNs: naltrexone hydrochloride/bupropion hydrochloride

Procedure number(s): EMEA/H/A-20/1530/C/3687/0065

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AEs	adverse events
AESI	adverse event of special interest
AUC	area under the curve
BMI	body mass index
BOCF	baseline observation carried forward
BP	blood pressure
bpm	beats per minute
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLI	comprehensive lifestyle intervention
Cmax	maximum plasma concentration
CV	cardiovascular
CVA	cerebrovascular accident
CVOT	cardiovascular outcome trial
DHPC	direct healthcare professional communication
DMC	data monitoring committee
DUS	drug utilisation study
EC	European Commission
EEA	European Economic Area
EHR	electronic health records
EMA	European Medicines Agency
EOS	end-of-study
EPAR	European public assessment report
ER	extended release
EU	European Union
FAERS	FDA Adverse Event Reporting Systems
FDA	Food and Drug Administration
HR	hazard ratio
IA	Interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRR	incidence rate ratio

ITT	intent-to-treat
LOCF	last observation carried forward
LS	least square
MACE	major adverse cardiovascular events
MAH	marketing authorisation holder
MI	myocardial infarction
mmHg	millimetres of mercury
N	number
OR	odds ratio
PASS	post-authorisation safety study
PP	per-protocol
PRAC	Pharmacovigilance Risk Assessment Committee
PY	patient years
RCT	randomised controlled trials
RMP	risk management plan
ROR	reporting odds ratio
RR	relative risk
SAEs	serious adverse events
SAP	statistical analysis plan
SAWP	Scientific Advice Working Party
SmPC	summary of product characteristics
SOC	system organ class
Tmax	time to maximum plasma concentration
US	United States

1. Information on the procedure

In July 2023, in view of the remaining concern on the potential long-term cardiovascular (CV) safety risk of Mysimba, and the lack of adequate study plan to address the uncertainty about this risk, the Committee for Medicinal Products for Human Use (CHMP) considered that a review of all available data on this risk and its impact on the benefit-risk balance of Mysimba in its approved indication needed to be conducted.

On 1 September 2023, the European Commission (EC) therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Mysimba and to issue, by 31 March 2024, a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked. In addition, the EC requested the CHMP to give its opinion, as to whether temporary measures were necessary to protect public health.

On 23 April 2024, additional time was required by the CHMP and EC extended the timelines for the delivery of the CHMP opinion to 31 July 2024. Further, on 31 May 2024, a new CHMP rapporteur was appointed, and the procedure was reset to Day 1. This entailed that the procedural steps that had taken place between 14 September 2023 and 30 May 2024 were annulled. In view of the additional time required by the CHMP to conduct the assessment from Day 1, the timelines for the adoption of the CHMP opinion were extended to 31 March 2025.

2. Scientific discussion

2.1. Introduction

Mysimba is a centrally authorised product containing a fixed-dose combination of naltrexone and bupropion. The exact neurochemical appetite suppressant effects of naltrexone and bupropion are not fully understood. Naltrexone is a mu-opioid antagonist and bupropion is a weak inhibitor of neuronal dopamine and norepinephrine reuptake. These components affect two principal areas of the brain, specifically the arcuate nucleus of the hypothalamus and the mesolimbic dopaminergic reward system.

Mysimba is indicated as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial body mass index (BMI) of:

- ≥ 30 kg/m^2 (obese), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension)

Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight. The need for continued treatment should be re-evaluated annually.

The product was granted a marketing authorisation in March 2015 based on results from four multicentre, double-blind, placebo-controlled obesity phase 3 studies (NB-301, NB-302, NB-303 and NB-304), demonstrating superiority of naltrexone/bupropion to placebo for the two co-primary endpoints (i.e. percent change from baseline body weight and the proportion of subjects achieving ≥5% total decreased body weight) measured at week 56 (NB-301, NB-302, and NB-304) or week 28 (NB-303). At the time of the evaluation of the marketing authorisation application , there were uncertainties regarding the true size of the effect given the high drop-out rate (around 50%), and the use of an imputation method for missing data which could have overestimated the treatment effect. However, when viewing the results of the primary endpoints as well as the secondary glycaemic and lipid-related endpoints in totality, the efficacy was considered to be clinically relevant.

In the phase 3 programme, naltrexone/bupropion was associated with transient relative mean increases in blood pressure (BP) (~1-2 mmHg) and in heart rate (~1.5 bpm) compared to placebo. Tachycardia was more commonly reported with naltrexone/bupropion than with placebo. In addition, myocardial infarction (MI) occurred more frequently in the naltrexone/bupropion group than in the placebo group, albeit the numbers were very small. In clinical practice, cases of hypertension have been reported with other bupropion-containing products, including some severe cases requiring acute treatment. It was further noted that post-marketing cases of hypertensive crisis had been reported during the initial titration phase with naltrexone/bupropion, and hypertensive crisis was identified as an adverse reaction in 2020.

During the assessment of the marketing authorisation application, a cardiovascular outcome trial (NB-CVOT; also referred to as the LIGHT trial) was ongoing and the first interim report of the study was submitted. The objective of the NB-CVOT study was to assess the occurrence of major adverse cardiovascular events (MACE) in overweight and obese patients with CV risk factors receiving Mysimba. The primary analysis of the intent-to-treat (ITT) population showed that statistically significantly more subjects treated with placebo (59 subjects, 1.3%) compared to naltrexone/bupropion (35 subjects, 0.8%) experienced MACE (hazard ratio [HR] [95% confidence interval (CI)] 0.59 [0.39-0.90]).

Although these interim results were reassuring in the short and intermediate term, uncertainty remained with respect to long-term CV safety given the limited exposure time in the study (~30 weeks) and the effects of naltrexone/bupropion on BP. Therefore, to further investigate the long-term CV safety of naltrexone/bupropion, the conduct of a multicentre, randomised, double-blind, placebo-controlled, phase 4 study to assess the effect of naltrexone/bupropion on the occurrence of MACE in overweight and obese subjects was requested by CHMP and imposed as a condition to the marketing authorisation. The results were due to be submitted by end of March 2022. However, this first NB-CVOT was terminated prematurely due to preterm unblinding.

A second CVOT study (NB-CVOT-2, also called NB-4001, or CONVENE) was initiated but also prematurely terminated in 2016. At that time, a third CVOT (NB-CVOT-3) was to be initiated to comply with the condition to the marketing authorisation. Annual progress reports were requested, but in November 2019, the NB-CVOT-3 study had still not been initiated.

In December 2020, based on data from the United States (US) showing that the majority (approximately 80%) of patients discontinued treatment with Mysimba prior to the stopping rule at 4 months, the marketing authorisation holder (MAH) claimed that the CVOT study, planned to be conducted in the US, was no longer feasible in its original design. Therefore, in 2021, the MAH proposed an alternative protocol: a health outcome study, designed as a retrospective database cohort study using electronic health records (EHR) as primary data source (EMEA/H/C/003687/ANX/001.6). This study design was not endorsed by the CHMP and its Scientific Advice Working Party (SAWP), as it was considered that this study would not provide relevant data regarding the long-term CV safety as required when the marketing authorisation of Mysimba was granted.

In January 2022, in the context of variation application EMEA/H/C/003687/II/0056, the MAH proposed another alternative protocol to replace the planned imposed CVOT study: a randomised, placebo-controlled, double-blind phase 4 pragmatic trial, intended to capture CV outcomes during the real-world use of naltrexone/bupropion after initial randomisation in order to assess the effect of naltrexone/bupropion on the occurrence of MACE in overweight and obese subjects with documented CV disease. The results of this study were not expected before 2027. During the variation procedure, the CHMP raised a number of concerns with the study design of this alternative study proposal, in particular with the sample size, the statistical methods and the milestone timelines. The protocol reviewed by CHMP was not considered acceptable since these concerns were not addressed. Overall, the CHMP, taking into account the view of the Pharmacovigilance Risk Assessment Committee (PRAC),

did not consider the proposed alternative study sufficient to generate robust evidence on the long-term CV safety of Mysimba. Additional risk minimisation measures proposed by the MAH were also considered insufficient to mitigate the potential CV risk for patients receiving long-term treatment and to overcome the need for a study investigating long-term CV safety.

In July 2023, in view of the remaining concern regarding the potential long-term CV safety risk of Mysimba, and the lack of adequate study plan to address the uncertainty about this risk, the CHMP considered that a review of all available data on this risk and its impact on the benefit-risk balance of Mysimba in its approved indication needed to be conducted. On 1 September 2023, the EC triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Mysimba and issue a recommendation on whether the marketing authorisation should be maintained, varied, suspended or revoked.

In the context of the Article 20 procedure, the CHMP considered all available data in relation to the CV safety of Mysimba, including non-clinical, clinical and post-marketing data, as well as from the literature presented by the MAH. Clinical and literature data in relation to efficacy was also considered. A summary of the relevant information is included below.

2.2. Data on safety

The MAH submitted data on the CV safety as well as data on BP and heart rate measurements from the phase 3 clinical studies assessed in the marketing authorisation, the two prematurely terminated CVOT studies (NB-CVOT [LIGHT] and NB-CVOT-2 [CONVENE]), post hoc analyses of the study data, health outcomes and drug utilisation studies, systematic literature reviews, meta-analyses and a cumulative review of all post-marketing spontaneous and solicited case reports from the MAH global safety database.

2.2.1. Patient exposure

In the clinical study programme, a cumulative total of 9,573 subjects were treated with naltrexone/bupropion and 7,184 subjects were treated with placebo through 11 October 2024. None of the clinical studies were conducted in the European Union (EU). Cumulatively, since the international birthdate of the product (i.e. 10 September 2014) until the data lock point of 31 July 2024, the post-marketing exposure was 716,257 patient years (PY), with 114,680 PY exposure in the European Economic Area (EEA). The MAH presented data on the Mysimba use in clinical practice including information on dose, duration of treatment and reasons for discontinuation.

In the NB-CVOT-1 (LIGHT) study, the study medication discontinuation rate was high (for the placebo arm: 3,738 subjects [84.0%]; for the naltrexone/bupropion arm: 3,339 subjects [74.9%]). A high percentage of patients who discontinued treatment remained in follow-up for MACE and contributed to the ITT analysis. The median duration of treatment was 16.3 weeks for placebo and 18.4 weeks for naltrexone/bupropion and the median time to study discontinuation was 139.0 weeks for placebo and 139.1 weeks for naltrexone-bupropion.

In the NB-451 drug utilisation study (DUS), the mean persistence of Contrave[1]/Mysimba use among the 22,182 individuals was 108 days. No information was made available on the overall reasons for treatment discontinuation, but information was provided for individuals who discontinued medication after an adverse event of special interest (AESI). Discontinuation was defined as not having a medication record (prescription and/or dispensing) for Contrave/Mysimba following the occurrence of an AESI. Unadjusted for background discontinuation rates, individuals taking Contrave/Mysimba had

[1] Brand name of authorised medicinal product in the US.

no medication records following neuropsychiatric events (409), suicidality events (50), non-fatal acute MI (15), severe hypersensitivity reaction (11), hepatotoxicity events (9), stroke (6) or seizure events (2).

To further assess the discontinuations rate for Mysimba, the MAH also conducted an analysis of pharmacy prescription data from 1 single US specialty pharmacy. Prescriptions dispensed for less than 3 months cumulatively with no additional dispensing were assumed to represent permanent discontinuations of treatment (for any reason). Conversely, prescriptions dispensed to an individual for 3 months or more cumulatively were categorised as recurring patients, regardless of any gaps in use. In this analysis, 46% of patients had less than 3 months dispensing and no additional prescriptions.

Lastly, the reported discontinuation rates in the literature are highly inconsistent, ranging from 0.2% to 86.7%. The relevance of these numbers is questioned, as both extremes are currently derived from conference abstracts. To note, Dong et al. (2017) reported a 1-year discontinuation rate of 49.1% for naltrexone/bupropion.

2.2.2. Clinical data

Phase 3 studies

The MAH provided post hoc analyses of MACE, systolic and diastolic BP, as well as heart rate overall and among early responders (at least 5% weight loss at week 16) and non-responders (<5% weight loss at week 16) in both ITT and per-protocol (PP) analyses of the phase 3 studies that supported the marketing authorisation of Mysimba. The ITT analysis set included all randomised subjects. The PP analysis set included all randomised subjects who received at least 28 weeks of study treatment, were ≥70% compliant with the study medication, had a baseline measurement, and at least 1 post-baseline body weight measurement while on study drug.

MACE events

A total of 7 MACE events were observed across the phase 3 studies. Out of these, 3 events were experienced by those receiving active treatment (naltrexone/bupropion) and 4 by those receiving placebo. No individual experienced more than one event. Three (3) MACE events occurred during the first 16 weeks of treatment and 4 events occurred between week 16 and week 56.

Blood pressure (BP) and heart rate

Naltrexone/bupropion was associated with less pronounced improvements in BP (systolic and diastolic) compared to placebo (difference: 1.4 mmHg for systolic and 0.5 mmHg for diastolic BP) in the pooled analyses of the phase 3 studies. Analyses by duration of treatment showed that the differences in BP between naltrexone/bupropion and placebo (1.7 and 1.4 mmHg for systolic and diastolic BP, respectively) were slightly greater during the first 16 weeks of treatment. The same trends and patterns were observed when using the ITT and PP analysis. In the subgroup of early responders, differences in BP were similar to the overall population (1.8 and 1.0 mmHg for systolic and diastolic BP, respectively). During the first 16 weeks of treatment, the difference in systolic and diastolic BP was 2.7 and 2.2 mmHg respectively.

Events of systolic BP>140 mmHg (43.3 versus 35.2 events per 100 PY) and diastolic BP>90 mmHg (60.1 versus 44.4 events per 100 PY) were increased for naltrexone/bupropion compared to placebo. The event rates of systolic BP>140 mmHg and diastolic BP>90 mmHg for both naltrexone/bupropion and placebo were greater during the first 16 weeks of treatment compared to week 16 and week 56.

Heart rate was decreased by 1 bpm in the placebo group and was close to baseline in the naltrexone/bupropion group (difference 1.3 bpm). Analyses by duration of treatment showed that the

difference in heart rate (2.0 bpm) between naltrexone/bupropion and placebo was slightly greater during the first 16 weeks of treatment. The same trends and patterns were observed when using the ITT and PP analysis. In the subgroup of early responders, the difference in heart rate was slightly larger (2.7 bpm). During the first 16 weeks of treatment, the difference in heart rate was 4.0 bpm (naltrexone/bupropion: +1.4 bpm and placebo: -2.6 bpm).

Events of pulse rate >90 bpm were slightly increased for naltrexone/bupropion compared to placebo (39.0 versus 32.3 events per 100 PY). The event rates of heart rate >90 bpm were greater during the first 16 weeks of treatment (65.2 versus 44.9) compared to week 16 until week 56 of treatment (22.6 versus 23.7) for Mysimba and placebo, respectively.

In addition to the pivotal phase 3 studies, results from the NB-404 (IGNITE) study, ongoing at the time of the marketing authorisation, were provided. IGNITE was a phase 3b, multicentre, randomised, open-label, controlled trial designed to assess the effects of naltrexone/bupropion in conjunction with a comprehensive lifestyle intervention (CLI) programme compared with usual care (diet, exercise education and study site recommendations) up to 78 weeks. The controlled treatment period lasted for 26 weeks. The study included a total of 242 subjects aged 18 to 60 years who had obesity (BMI from 30 to 45 kg/m^2) or were overweight (BMI ≥27 kg/m^2) and had dyslipidaemia, controlled hypertension, or both. In this study, 153 patients were randomized to receive naltrexone/bupropion+CLI and 89 were randomized to receive usual care.

At baseline, mean systolic BP measurements were 120.9 mmHg in the usual care group and 125.1 mmHg in the naltrexone/bupropion+CLI group. At endpoint (week 26), mean systolic BP decreased from baseline in both groups, with a numerically greater decrease observed in the naltrexone/bupropion+CLI group than the usual care group (least square (LS) mean of -4.8 mmHg versus -2.8 mmHg), and the magnitude of the treatment difference (naltrexone/bupropion+CLI minus usual care) was -2.0 mmHg (95% CI [-4.9 to 0.9]). From baseline through week 78 (week 78 PP population), treatment with naltrexone/bupropion+CLI showed a mean change in systolic BP of -2.7 mmHg.

At baseline, mean diastolic BP measurements were 79.0 mmHg in the usual care group and 80.5 mmHg in the naltrexone/bupropion+CLI group. At endpoint (week 26), mean diastolic BP decreased from baseline in both groups, with a numerically greater decrease observed in the naltrexone/bupropion+CLI group than the usual care group (LS mean of -1.7 mmHg versus -1.3 mmHg), and the magnitude of the treatment difference (naltrexone/bupropion+CLI minus usual care) was -0.4 mmHg (95% CI [-2.6 to 1.8]). The mean change in diastolic BP from baseline through week 78 (week 78 PP Population) for the naltrexone/bupropion+CLI was –1.7 mmHg.

CVOT studies

NB-CVOT-1 (LIGHT)

The NB-CVOT-1 (LIGHT) study was designed with primary and secondary endpoints suitable to investigate the CV safety of long-term treatment with naltrexone/bupropion. The primary endpoint of this study was time to a first event within the primary MACE composite (CV death, nonfatal MI, or nonfatal stroke). Two pre-planned interim analyses (IA) were conducted on this endpoint, IA1 (25% interim analysis) and IA2 (primary, 50% interim analysis), as well as an analysis using the totality of data following IA2. The study was terminated prematurely shortly after IA2 (50%).

The previously assessed analyses of the ITT population of the NB-CVOT-1 showed HR estimates for MACE of 0.59 (95% CI [0.39-0.90]), 0.88 (95% CI [0.57-1.34]) and 0.95 (95% CI [0.65-1.38]), respectively, for the analysis of 25% interim data, 50% interim data and the final analysis of data

(64% of data), respectively. A total of 264 MACE events were included in the totality of data. The number of patients on-treatment for 24 months was >1990 (naltrexone/bupropion=~1200; placebo=~770).

In the context of the present review, the MAH submitted new analyses by study duration. In these analyses, there were 243 MACE events, with >3% of subjects having an event over any study duration. The HR estimate (all time) was found to be 0.96 (95% CI [0.74-1.24]). The HR point estimates were 0.61 (95% CI [0.29-1.29]), 0.62 (95% CI [0.39-0.98]) and 0.73 (95% CI [0.47-1.14]), respectively, at ≤16 weeks, 16-52 weeks, and 52-104 weeks, respectively (see Table 1). However, these analyses did not consider treatment discontinuation. The on-treatment information was lower (overall 86 events) (Nissen et al. [2016]) and scarce when considering only the events in the second or third year (end-of-study [EOS] analysis on treatment: 56 events in the first year [27 naltrexone/bupropion, 29 placebo], 18 events in the second year [13 naltrexone/bupropion, 5 placebo] and 12 events in the third year [7 naltrexone/bupropion, 5 placebo]).

Table 1 - Risks and rates of MACE among active and placebo groups in the LIGHT trial

	All time	**≤16 weeks**	**>16 and ≤52 weeks**	**>52 and ≤104 weeks**
Active (naltrexone/bupropion)				
N events/N subjects	119/4450	11/4450	31/2535	41/1578
Person years	4,424.30	1,055.49	1,305.16	1,352.87
Event rate	0.0269	0.0104	0.0238	0.0303
Risk of event	2.67%	0.25%	1.22%	2.60%
Placebo				
N events/N subjects	124/4444	18/4444	45/2278	39/1096
Person years	3,504.72	1,181.41	934.82	905.03
Event rate	0.0354	0.0152	0.0481	0.0431
Risk of event	2.79%	0.41%	1.98%	3.56%
Relative Risks				
IRR (95% CI)	0.76 (0.59, 0.98)	0.68 (0.32, 1.46)	0.49 (0.31, 0.79)	0.70 (0.45, 1.10)
Risk Ratio (95% CI)	0.96 (0.74, 1.23)	0.61 (0.29, 1.29)	0.62 (0.39, 0.98)	0.73 (0.47, 1.14)

Note: For analyses by duration of treatment exposure, the first occurrence of each MACE for each subject was allocated to the corresponding treatment exposure interval in which the event took place.
Abbreviations: IRR = Incidence rate ratio; CI=confidence interval; MACE=Major cardiovascular events; N=number.

For BP and heart rate, the analyses by duration of treatment were also presented. During the first 16 weeks of treatment, there were slight increases in BP and heart rate in both treatment groups with slightly elevated in BP (0.3 and 0.2 mmHg for systolic and diastolic BP, respectively) and heart rate (0.7 bpm) observed in the naltrexone/bupropion group compared to placebo. In early responders, differences in BP were slightly greater (0.8 and 0.3 mmHg for systolic and diastolic BP, respectively) whereas differences in heart rate (2.0 bpm) were higher for naltrexone/bupropion compared to placebo. Events of systolic BP >140 mmHg (29.7 versus 26.4 events per 100 PY), diastolic BP >90

mmHg (15.0 versus 13.3 events per 100 PY) and pulse rate >90 bpm (12.8 versus 10.2 events per 100 PY), respectively, were slightly more increased for placebo compared to naltrexone/bupropion.

Among subjects who had data captured after week 52, the mean changes from baseline in systolic BP, diastolic BP, and heart rate were minimal in both placebo and active treatment groups. Specifically, the mean changes were <3.5 mmHg for systolic BP, <2.0 mmHg for diastolic BP, and <1.1 bpm for heart rate, with differences between the active and placebo groups from baseline being <1.0 mmHg, <0.8 mmHg, and <0.5 bpm, respectively. Additionally, subjects receiving long-term active treatment experienced fewer events of elevated systolic BP (>140 mmHg), diastolic BP (>90 mmHg), and pulse rate (>90 bpm) compared to those receiving placebo, as indicated by the point estimates of the risk ratios and incidence rate ratios, however, differences seemed minimal. These results could be considered further limited by the fact that patients discontinuing treatment but staying within the study were included in the analysis.

NB-CVOT-2 (CONVENE; NB-4001)

This study was the second CVOT planned to assess the effect of naltrexone/bupropion on the occurrence of MACE in overweight and obese subjects with CV disease. Limited data is available since this study was terminated early. At the time of the early study termination, the mean durations on study medication during the treatment period was about 4 weeks (3.98 weeks in the naltrexone/bupropion group and 4.14 weeks in the placebo group). No MACE, BP or heart rate data is available. Additionally, only a limited number of adverse events (AEs) were recorded, which are deemed to have limited significance.

2.2.3. Real-world data

Health outcomes analysis

The MAH conducted a non-interventional study to generate real-world evidence on the CV safety of Contrave[2]/Mysimba in the US. This health outcomes analysis, conducted using a US de-identified EHR dataset, was completed in July 2023. The primary objective of this analysis was to compare the incidence of non-fatal acute MI and stroke between Contrave/Mysimba and an active comparator (lorcaserin). The study population included patients from 18 years of age, restricted to subjects with a healthcare encounter within 180 days prior to the medication record date. The longitudinal coverage of patients and the ability to reliably capture exposure and outcomes was considered uncertain since the data extraction only covered certain healthcare providers and was not population-based.

The analysis was based on 12,475 initiations for Contrave/Mysimba and 12,171 for lorcaserin. The mean age was 48 years. The proportion with missing data was high for some variables. There were 26 acute MI, 6 stroke, and 31 combined MACE outcomes in the Contrave/Mysimba group, compared to 36 acute MI, 5 stroke, and 40 combined MACE outcomes in the lorcaserin group. Rates of MACE were similar between Contrave/Mysimba and lorcaserin (HR 0.76, 95% CI [0.48, 1.20]). Rates of acute MI (HR 0.74, 95% CI [0.45, 1.23]) and stroke (HR 1.05, 95% CI [0.34, 3.22]) were also similar. The mean follow-up was ~1,700 days in the ITT analysis but only 120 days in the as-treated analysis. This means that the duration of exposures was overall too short to be relevantly influenced by the exposure to treatment. Consequently, most MACE events observed were likely reflecting the background risk.

[2] Brand name of authorised medicinal product in the US.

Drug utilisation and safety study (DUS) NB-451

The DUS NB-451 aimed to characterise the 18-month real-world utilisation patterns of Mysimba. One of the secondary objectives of this study was to quantify patients who were compliant with the product information and, among these, those who did experience an AESI during follow-up including MACE ascertained without data on death status (ischaemic stroke, haemorrhagic stroke, or acute MI). The European part of this study is still ongoing. In the Mysimba cohort, CV events were not considered frequent, with 11 events of acute MI (0.3 events per 1,000 PY) and 4 events of stroke (0.1 events per 1,000 PY). The BP analysis of the complete cases from this study showed an increase from baseline in both systolic (2 mmHg) and diastolic (1 mmHg) BP in subjects initiating Contrave/Mysimba treatment. The magnitude of the increase of 2 mmHg systolic and 1 mmHg diastolic was greater than what was observed in the clinical trials.

2.2.4. Post-marketing data

A broad search of all spontaneous and solicited case reports in the MAH global safety database retrieved a total of 1,991 events (267 serious events and 1,724 non-serious events) within 1,818 cases under the system organ class (SOC) cardiac disorders and the SOC vascular disorders. Out of these, 241 were unique cases corresponding to 267 serious events. These 241 unique cases were further adjudicated manually by 4 physicians as MACE, MACE+ (including coronary, cerebrovascular, and peripheral revascularisation events or hospitalisation for heart failure) and hypertensive crisis. As a result, a total of 156 potential cases were identified under the 4 MACE categories (fatal MACE, non-fatal MI, non-fatal cerebrovascular accident [CVA], MACE+) and the category of hypertensive crisis.

Fatal MACE

A total of 20 fatal potential cases of MACE were retrieved. All the fatal event cases were reviewed in detail for MACE events. Of the 20 potential cases, 10 cases were considered appropriate to assess for MACE causality relationship. No cases were considered probably related, 5 cases were considered possibly related, 1 case was considered unlikely related, and 4 cases were considered not possible to assess.

Non-fatal MI

A total of 35 non-fatal potential cases of MI were retrieved. All cases were assessed for the required terminology that was consistent with an MI, required hospitalisation, reporting by a healthcare professional (HCP) or terminology consistent with HCP description, laboratory, electrocardiogram, or procedure including stent angioplasty revascularisation evidence. Of the 35 non-fatal potential cases, 4 cases reporting MI (n=3) and acute MI (n=1) were considered appropriate to assess for causality relationship. No cases were considered probably related, 1 case was considered possibly related, 1 case was considered unlikely related, and 2 cases were unclassifiable.

Non-fatal cerebrovascular accident (CVA)

A total of 49 non-fatal potential cases of CVA were retrieved. All cases were assessed for the required terminology that was consistent with a CVA, required hospitalisation, reported by HCP or terminology consistent with HCP description, laboratory, or radiographic evidence. Of the 49 non-fatal potential cases, 12 cases were considered appropriate to assess for causality relationship. No cases were probably related, 1 case was possibly related, 4 cases were unlikely related, and 7 cases were unclassifiable.

MACE+

A total of 15 MACE+ potential cases were retrieved plus 1 potential case also captured under non-fatal. Of the 16 potential cases, 2 cases reporting the terms "coronary artery disease", "oedema", and "diastolic dysfunction" were considered appropriate to assess for causality relationship. One case was considered possibly related and 1 case was unclassifiable.

Hypertensive crisis

A total of 36 potential cases of hypertensive crisis were retrieved. A manual review of all serious and HCP-confirmed events was completed to exclude the occurrences if the reported information did not provide evidence at a minimum of BP values of >180 mmHg systolic or >120 mmHg diastolic. Of the 36 potential cases, 7 cases were considered appropriate for review and causality assessment. One case was probably related, 2 cases were possibly related, 1 case was unlikely related and 3 cases were not possible to assess or considered unclassifiable.

2.2.5. Literature

A cumulative literature search concerning CV safety of Mysimba was conducted and the relevant articles are summarised below.

Nissen et al. (2016) published the 25% and 50% interim data, including EOS data, from NB-CVOT-1 (LIGHT) study. The relevant data from this study provided by the MAH is presented in section 2.2.2.

Gorelik et al. (2020) conducted a study using the Food and Drug Administration (FDA) Adverse Event Reporting Systems (FAERS) database to evaluate CV signals associated with anti-obesity drugs. The authors analysed data from January 2013 to December 2018, focusing on lorcaserin, naltrexone/bupropion, phentermine, and phentermine-topiramate. A disproportionality analysis revealed that naltrexone/bupropion had a significantly lower proportion of CV AEs compared to other products (reporting odds ratio (ROR)= 0.58; 95% CI [0.49-0.70]), with no safety signal for major CV events such as MI, stroke, CV death, cardiac failure, or arrhythmia.

Onakpoya et al. (2020) performed a meta-analysis of unpublished clinical study reports to compare the benefits and risks of naltrexone/bupropion. The authors searched the FDA and EMA websites, PubMed, and ClinicalTrials.gov to identify the pivotal phase 3 trials. Their analysis indicated that naltrexone/bupropion increased the risk of AEs (relative risk (RR)= 1.11; 95% CI [1.05-1.18], P=0.0004), serious adverse events (SAEs) (RR= 1.70; 95% CI [1.38-2.10], p<0.00001), and treatment discontinuation due to AEs (RR= 1.92; 95% CI [1.65-2.24], p<0.00001).

Sposito et al. (2021) conducted a systematic literature review and meta-analysis of 12 phase 3 randomized controlled trials evaluating bupropion, naltrexone, or in combination. Using an additive network meta-analysis model for random effects, the authors found no significant difference in the incidence of MACE between treatment groups. The odds ratios (OR) for MACE were 0.90 (95% CI [0.65-1.25], p=0.52) for bupropion, 0.97 (95% CI [0.75-1.24], p=0.79) for naltrexone, and 1.08 (95% CI [0.71-1.63], p=0.73) for their combination, indicating no increased risk.

Alsuhibani et al. (2022) analysed the FAERS database from January 2013 to June 2020 to estimate and characterise the frequency of AEs associated with anti-obesity medications. They found that most AEs associated with naltrexone/bupropion were nausea (27%), vomiting (27%), dizziness (22%), headache (22%), insomnia (19%), and anxiety (17%), with CV disease reported in a lower proportion (7%) compared to other drugs.

Dahlberg et al. (2022) assessed studies reporting MACE and other CV events through a systematic literature review. The authors included 70 studies, with half reporting no CV events and the other half

reporting a non-zero frequency of CV events. The analysis concluded that there was no increased risk of CV events or MACE following the use of naltrexone/bupropion ER, naltrexone with bupropion, or of the individual components.

Dutta et al. (2022) conducted a health outcomes study in patients with obesity (BMI ≥35 kg/m²) and type 2 diabetes undergoing medical weight management from 2010 to 2021. They compared medical weight management (including naltrexone/bupropion), metabolic/bariatric surgery, and control groups, focusing on a 6-component MACE as the primary outcome. The study found no difference in MACE between medical weight management and control (HR= 1.15; 95% CI [0.83-1.59], p=0.40), but a higher risk compared to metabolic/bariatric surgery (HR= 1.72; 95% CI [1.06-2.77], p=0.03).

Iannone et al. (2023) performed a systematic review and random-effects network meta-analysis of 168 trials (97,938 patients) evaluating medicinal products approved for treating obesity and overweight patients. The analysis showed that naltrexone/bupropion was associated with a lower CV mortality compared with placebo (OR= 0.62; 95% CI [0.39-0.99]).

2.2.6. Discussion on safety

The MAH presented data from various sources to support the CV safety of Mysimba. This included information previously assessed, new studies and new analyses from previous studies. The data in the pooled analyses of the pivotal phase 3 studies confirmed the safety profile known at the time of Mysimba's marketing authorisation, both in terms of identified risks and uncertainties. In these analyses, similarly to what was observed at time of the evaluation, Mysimba was associated with less pronounced reductions in BP (systolic and diastolic) compared to placebo (difference: approximately 2 mmHg in systolic BP and 1 mmHg in diastolic BP). Heart rate decreased by 1 bpm in the placebo group whereas heart rate in the Mysimba group was close to baseline. Further, when assessing the data based on treatment duration, the magnitude of the differences in BP and heart rate changes between Mysimba and placebo were greater during the first 16 weeks of treatment compared to between weeks 16 and 56. In the same pooled analyses, the low numbers of MACE observed were not indicative of a difference between the active and placebo treatments over the duration of the phase 3 trials.

The safety results above pertain to data up to 1 year of treatment. Beyond this period, data is limited and comes primarily from the NB-CVOT-1 study. In the new analyses provided for this study based on duration of treatment, the HR estimate (all time) for MACE was found to be 0.96 (0.74, 1.24). The HR point estimate was 0.61 (0.29, 1.29), 0.62 (0.39, 0.98) and 0.73 (0.47, 1.14), respectively, at ≤16 weeks, 16-52 weeks, and 52-104 weeks. These HR point estimates for MACE in the NB-CVOT-1 study do not support an increased risk for MACE. Slight increases in BP and heart rate were experienced during the first 16 weeks of treatment with both Mysimba and placebo groups, and with Mysimba showing slightly higher increases. However, the differences with placebo were minor. Additionally, events of elevated systolic and diastolic BP, as well as pulse rate, were slightly more frequent in the placebo group compared to Mysimba. Overall, Mysimba had a marginally greater impact on heart rate, particularly in early responders, but the overall differences in CV measures between the two groups were relatively small. For longer periods, both the placebo and active treatment groups showed minimal changes in systolic and diastolic BP, as well as heart rate after 52 weeks of treatment. The differences between the placebo and active treatment groups were minimal. Less events of elevated BP and heart rate were observed in the active treatment group compared to the placebo group. Overall, it was considered that the data from the NB-CVOT-1 study, while not raising concerns with the long-term CV safety, are not sufficiently reliable to fully demonstrate the long-term CV safety of Mysimba. This is due to the methodological limitations derived from the early discontinuation of the study. The precision of the estimated risk is substantially reduced considering that the number of MACE captured was lower than planned.

In addition to the clinical trial data, some non-interventional studies on CV safety were provided. This included the completed health outcome analysis, based on 24,600 patients with an average follow-up of over 1,700 days that did not reveal any evidence of excess CV risk between Mysimba and the comparator group (lorcaserin). In another non-interventional study, the DUS NB-451, CV events were not common in the Mysimba cohort, with 11 (0.3 events per 1,000 PY) and 4 (0.1 events per 1,000 PY) events for acute MI and stroke, respectively. Despite these results, the robustness of the data sources of these studies was questioned. The health outcome analysis has severe methodological limitations for estimating the CV risk. The study design and data used do not have sufficient sensitivity and validity to detect a relevant MACE risk. Additionally, the DUS was not designed to assess the long-term safety of Mysimba. It is a descriptive database study without a comparator group. The value of evaluating CV safety data from this study was therefore considered limited. In summary, while the results of these studies do not raise concerns, they also do not provide additional reassurance regarding the CV safety of Mysimba.

A total of 156 potential cases were identified in the cumulative review of MACE and related CV events from the post-marketing sources identified (20 fatal MACE, 35 non-fatal MI, 49 non-fatal CVA, 16 MACE+ [including unstable angina requiring hospitalisation and coronary revascularisation procedure] and 36 hypertensive crisis). Most cases reviewed had an unknown or short (<36 days) time to onset. Spontaneous reports have several limitations due to underreporting, missing clinical information and lack of a control group. Therefore, this cumulative review does not inform on the long-term CV safety. The same can be concluded from the data reported in the literature. Generally, from the available literature reviews and meta-analysis, it seems that naltrexone/bupropion does not appear to significantly increase the risk of major CV events compared to other treatments. However, the publications have limited value with respect to the long-term CV safety of Mysimba, as they rely on spontaneous reporting, are underpowered and have short observation periods.

In conclusion, no data has arisen to reliably address the remaining uncertainty related with the long-term CV risk. The data reviewed, including additional post hoc analyses of the phase 3 studies and early terminated CV studies, as well as from non-interventional studies, do not allow to fully characterise the long-term CV safety of Mysimba. Therefore, the uncertainties regarding long-term CV safety beyond 1 year of treatment still need to be addressed with data coming from a CVOT, as per the condition to the marketing authorisation.

To address the uncertainty related to the long-term CV risk and fulfil their obligation, the MAH proposed the NB-CVOT-3 study (INFORMUS)[3]. This study was initiated in the US while the present review was ongoing. As of 31 January 2025, 2,825 patients had been randomised. The study is a phase 4, multi-centre, prospective, randomized, pragmatic, double-blinded, placebo-controlled study intended to capture CV outcomes in clinical practice. Its primary objective is to evaluate the CV safety of patients receiving naltrexone/bupropion compared with placebo to estimate the risk of MACE when given in combination with standard of care (real-world setting) to subjects with obesity or who are overweight and have an increased risk of adverse CV outcomes. Secondarily, the study will assess the comparative rates of MACE component events (i.e. CV death, non-fatal MI, and non-fatal stroke).

The study plans to build on the results from the NB-CVOT-1 (LIGHT) study and a Bayesian statistical approach will be employed for the primary and secondary endpoint analyses using a prior based on the results from the LIGHT study. For this purpose, a prior distribution centred around a HR=1 and a variance corresponding to a 75% discount of the 50% IA of the LIGHT trial will be primarily considered. This approach requires approximately 212 new events in a new study such that the combined information (prior + new data) would have approximately 80% power to fulfil the decision rule of Pr(HR<1.4)>0.975 (where HR is the posterior HR) in the event that HR≈1. The primary analysis

[3] NCT06098079; Available at: https://clinicaltrials.gov/study/NCT06098079

will first test for non-inferiority. If the test of non-inferiority is successful, then the primary endpoint will be tested for superiority using a frequentist 95% CI analysis. Approximately 8,600 subjects will be enrolled and randomised into the study. It is estimated that 5,000 subjects (2,500 in the active arm and 2,500 in the placebo arm), after attrition, are required to achieve the number of required outcomes to meet study endpoints. Subjects will be followed from treatment initiation through 1 year following treatment termination. A treatment policy strategy is suggested for treatment discontinuation for the primary estimand considering events of patients who stopped treatment. An independent data monitoring committee (DMC) will complete an unblinded review of data when approximately 50% of the 212 MACE outcomes have been adjudicated. The primary purpose of the DMC is to assess benefit-risk balance across both treatment arms and assess overall safety. This will not be an IA as stopping the trial due to study success is not foreseen. The setup and conduct of the DMC and data analysis will be detailed in the DMC charter.

The CHMP reviewed earlier protocol proposals of this study in variation EMEA/H/C/003687/II/0056 (see Section 2.1. for background) which were not considered sufficient to generate robust evidence on the long-term CV safety of Mysimba. In the context of the current procedure, the CHMP assessed the protocol of the NB-CVOT-3 study and requested the MAH to clarify certain elements and amend the protocol accordingly. It was acknowledged that the study was ongoing.

The possibility of expanding the sample size and specify a minimum follow-up was discussed. However, no minimum follow-up period was specified in this event-driven trial and the MAH argued based on modelled scenarios assuming different discontinuation rates that the trial's projected follow-up exceeds two years for (almost) all patients. However, the simulations assumed that patients discontinuing treatment and having an event are not counted anymore which is not the case when applying a treatment policy strategy for treatment discontinuation. Despite the CHMP's request, the protocol was not amended to include a minimum follow-up period of 2 years or an extended follow-up for patients who discontinue study treatment. Nevertheless, the CHMP noted that it is the responsibility of the MAH to ensure the generation of long-term data in accordance with the provided simulations and address their obligation.

Additionally, the power of the study using a Bayesian approach was questioned. Overall, the CHMP noted that there is no scientific or regulatory justification to reject a Bayesian analytical approach as a principle. In line with ICH E9, the use of Bayesian approaches "*may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust*".[4] However, the impact of prior information was not investigated by presenting appropriate simulations and the non-feasibility of the frequentist approach was not shown by the MAH. Therefore, the frequentist analysis approach, without borrowing of data, was still considered by CHMP of equal importance and should lead to similar conclusions for a robust interpretation of the study results. If not provided by the MAH with the study results, simulations concerning the frequentist operating characteristics (Type I error and Type II error) for the Bayesian decision criterion for different analysis priors (sceptical, enthusiastic and non-informative), especially also for the prior defined for the primary analysis, will be requested by CHMP once the study results are available. It is essential that the commensurability of the historical and new data is evaluated, and sensitivity analyses using weakly and non-informative priors are provided, to contextualise the study results. The MAH acknowledged this request and committed to consider incorporating necessary and appropriate changes in future amendments to the statistical analysis plan (SAP).

In terms of study endpoints, as requested, the MAH amended the study protocol to include an expanded MACE endpoint as new secondary endpoint ("MACE+" consisting of MACE or any coronary,

[4] In this respect, see section 1.2 of the guideline titled, "ICH Topic E9 on Statistical Principles for Clinical Trials – Step 5 – NOTES FOR GUIDANCE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS (CPMP/ICH/363/96) of September 1998.

cerebrovascular and peripheral revascularisation events, or hospitalisation for heart failure). Also, the MAH proposed several updates to the protocol concerning study operations to mitigate potential misclassification of cause of death and loss-to-follow-up without known cause. Additional endpoints (all-cause death and time to all-cause death) and sensitivity analyses were added due to the potential for informative censoring either due to death (treating non-CV death with a composite strategy) or due to loss of follow-up (multiple imputation of MACE times for patients' loss-to-follow-up under various assumptions about the censoring mechanism and a tipping point analysis based on the approach described in Zhao, 2014). To address the issue of competing risks raised by CHMP, such as when death precedes other events, cumulative incidence functions will be estimated using the Aalen-Johansen method (Aalen and Johansen, 1978). This approach provides a more precise understanding of event frequency over time by acknowledging that death can preclude the observation of subsequent events.

The importance of appropriately handling intercurrent events, specifically treatment discontinuation and rescue medication, which may occur differently in the context of non-inferiority and superiority comparisons, was also acknowledged by CHMP. For the non-inferiority objective, the estimand applying a hypothetical strategy for treatment discontinuation or rescue medication is seen as equally important to the primary estimand applying a treatment policy strategy for these intercurrent events. In response to this concern, the MAH has committed to leverage sensitivity analyses in the current SAP to help address the different needs of superiority and non-inferiority comparisons. Overall, the CHMP considered that the proposed additional sensitivity analyses improve the ability to evaluate the consequences of discontinuation of randomised treatment.

Lastly, the MAH has committed to ensure timely execution and completion of the INFORMUS study to further characterise the long-term CV safety of Mysimba. The results of the study are due to be submitted by 31 December 2028. Additionally, the MAH will submit annual reports on the study progress. The first annual progress report, including the DMC charter outlining the setup and conduct of the planned DMC data analyses, will be submitted one year after adoption of the CHMP opinion on the present procedure. Additionally, the annual reports should discuss the rate of enrolment to ensure a timely completion of study. Further, the number of randomised patients, the number and proportion of patients permanently discontinuing treatment, and the number and proportion of participants who withdrew consent or were lost to follow-up should also be provided.

2.3. Data on efficacy

The MAH submitted previously assessed data on efficacy (dose response studies OT-101 and NB-201, pivotal studies NB-301, NB-302, NB-303, and NB-304, and supportive studies NB-431, NB-401, NB-402, and interim results from the NB-CVOT-1 [LIGHT]). New data included results from clinical studies on long-term clinical benefits beyond 1 year (final analysis of NB-CVOT-1 [LIGHT] and the open label extension study NB-404 phase 3b [IGNITE]) and from published literature. Additional post hoc supplementary analyses for the pivotal phase 3 studies using all randomised patients, including a treatment policy strategy for treatment discontinuation and reference based multiple imputation for missing data, were also provided.

2.3.1. Clinical data

Post hoc supplementary analysis of the phase 3 studies

The co-primary efficacy-related endpoints (percentage weight loss from baseline at week 56 and ≥5% weight loss at week 56), as well as the key efficacy secondary endpoint (≥10% weight loss at week 56) were evaluated for each study (NB-301, NB-302, NB-303, and NB-304) as well as for the pooled studies in post hoc supplementary analyses of the treatment effect of naltrexone/bupropion. These

analyses used all randomised patients including a treatment policy strategy for treatment discontinuation and reference based multiple imputation for missing data. The results showed treatment differences between naltrexone/bupropion and placebo more modest compared with the analyses originally performed using last observation carried forward (LOCF). Nevertheless, the reported outcomes of the weight change from baseline analyses as well as from the ≥5% and ≥10% weight loss responder analyses, were all in favour of naltrexone/bupropion. The results using reference based multiple imputation were similar to results using baseline observation carried forward (BOCF), where results were considered modest, but still clinically relevant when granting the marketing authorisation.

NB-CVOT-1 (LIGHT)

This study was not designed to assess long-term efficacy on the reduction in body weight as either a primary or secondary endpoint. However, in the exploratory analysis of change in body weight presented by the MAH, at 52 weeks, a greater LS mean percent change in body weight was observed with naltrexone/bupropion (-3.1%; 95% CI [-4.8, -1.4]) when compared with placebo (-0.3%; 95% CI [-1.9, 1.4]). With respect to effect beyond 1 year, at 104 weeks, on-treatment LS mean percent change in body weight was -6.3% with naltrexone/bupropion (95% CI [-7.0, -5.7]; n=1137) vs -3.5% with placebo (95% CI [-4.2, -2.8]; n=741). The results in the ITT population at this time point were -3.15 vs -1.34% with a difference -1.81 (-2.33, -1.30). The NB-CVOT-1 results showed PP LS mean percent weight loss of - 7.85 kg, -7.00 kg, and -6.56 kg at 52, 104, and 208 weeks, respectively. The corresponding long-term placebo control data at 52, 104, and 208 weeks are -4.19, -3.84, and -3.53. Hence, the LS mean differences in the PP population at 52, 104, and 208 weeks are -3.66 kg (95% CI [-4.15, -3.17]), -3.16 kg (95% CI [-3.82, -2.49]), and -3.03 kg (95% CI [-3.87, -2.19]). Notably, as presented before, the discontinuation rate in this study was high with only 38% of patients being on treatment after 1 year.

Study NB-404 Phase 3b (IGNITE)

The primary endpoint of the NB-404 phase 3b (IGNITE) was the percent change in weight from baseline to week 26 in the PP population. The naltrexone/bupropion + CLI subjects lost significantly more weight than usual care subjects at week 26 (8.52% difference; p <0.0001). The mean percent change at 52 weeks for usual care/naltrexone/bupropion+CLI was -9.21% and for naltrexone/bupropion+CLI -10.54% (LS mean difference: -1.31, 95% CI [-4.26, 1.64]). The mean percent change at 78 weeks for usual care/naltrexone/bupropion+CLI was -10.22% and for naltrexone/bupropion+CLI was -9.22% (LS mean difference: 1.24, 95% CI [-2.37, 4.84]).

2.3.2. Literature

A number of publications between 2010 and 2024 were identified by the MAH, either analysing the pivotal trials data in a post hoc setting or using observational data. The publications included randomised controlled trials (RCTs), single arm trials, pooled analyses, and retrospective cohort studies. The durations of the prospective studies varied from 1 to 18 months and the number of participants from only a few subjects to more than 2000 in some of the pooled analyses.

Pooled RCT analyses in patients taking naltrexone/bupropion (Apovian, 2013, Halseth, 2015) reported approximately 7% weight loss at 13 months. These analyses were mainly based on the pivotal studies from the marketing authorisation. With respect to long-term data, there is a publication by Calderon et. al, (2022) referring to a retrospective collection of data from electronic medical records of patients with obesity prescribed with weight lowering treatment for long-term use in academic and community multi-disciplinary weight loss programmes between January 2016 and January 2020. The study included 304 patients out of which 52 patients completed 24 months follow-up. The weight loss in the

naltrexone/bupropion group at this time point was -12%. However, this result was based on only 10 patients.

2.3.1. Discussion on efficacy

At the time of the marketing authorisation of Mysimba, the CHMP concluded that the efficacy of Mysimba in weight management was limited, but when reviewing the results of the primary endpoints as well as the secondary glycaemic and lipid-related endpoints in totality, it was considered to be clinically relevant. The additional data submitted in the present review do not contradict this conclusion.

With respect to the phase 3 studies, considering the vast number of subjects who discontinued study treatment in the pivotal studies (i.e. approximately 40-50%, similarly between active and control arms), it is not unexpected that the treatment differences between naltrexone/bupropion and placebo in the post hoc analyses provided for the present review were more modest compared with the analyses originally performed. However, despite the impact on the estimates of including all randomised subjects and using a reference based multiple imputation or BOCF, the reported outcomes from the weight change from baseline analyses as well as from the ≥5% and ≥10% weight loss responder analyses, were all in favour of Mysimba. The results using reference based multiple imputation were similar to BOCF analysis, for which results were considered modest, but still clinically relevant when granting the marketing authorisation.

In the ITT set of the NB-CVOT-1 (LIGHT) study, the treatment effect at week 52 was slightly lower compared to the results of the pivotal phase 3 trials and the difference in % weight change diminished to -1.81 (-2.33, -1.30) at week 104. In all analyses presented, the weight loss in % from baseline beyond 1 year, the proportion of subjects with ≥5% weight loss from baseline and the proportion of subjects with ≥10% weight loss were higher when compared to the placebo group. It can be assumed that when using reference-based multiple imputation or BOCF, the treatment effects may have been lower. Very scarce efficacy data were provided for an even longer treatment period. The LS mean differences in the PP population for weight loss at 52, 104, and 208 weeks were -3.66 kg (95% CI [-4.15, -3.17]), -3.16 kg (95% CI [-3.82, -2.49]), and -3.03 kg (95% CI [-3.87, -2.19]). For the ITT population, using an appropriate imputation method these values are likely lower.

When looking at other data sources, the IGNITE study results provided only limited insight into the long-term efficacy of Mysimba beyond 1 year. Likewise, while the literature data submitted is acknowledged, it suffers from several limitations that preclude reliable conclusions, since these studies either evaluated the pivotal trials in a post hoc setting or used observational data.

2.4. Non-clinical data

Overall, no new relevant non-clinical data were available. The CV effects of naltrexone and bupropion observed in the non-clinical studies do not show cause for concern, and the safety profile should therefore rely on the short, medium, and long-term clinical evidence and safety information. This is in alignment with the conclusions drawn at time of the marketing authorisation. In general, exposure data for naltrexone/bupropion (AUC, Cmax, Tmax) to support translation of the non-clinical data to the clinical situation is limited and/or has not been presented by the MAH and therefore comparing non-clinical and clinical exposure has not been done. This was accepted during the assessment of the marketing authorisation in 2015 (EPAR, EMA/805547/2015). Hence, echoing conclusions from the 2015-approval, the available non-clinical data supports short- to medium-term administration in humans. However, with regards to the long-term CV safety profile of Mysimba, long-term human administration cannot be evaluated based on non-clinical data and must rely on the clinical study data.

3. Benefit-risk balance

The CHMP considered the data submitted by the MAH in relation to the long-term CV safety and efficacy of Mysimba in its authorised indication. This included data from the pivotal clinical trials, additional post hoc analysis, data from the early-terminated NB-CVOT-1 (LIGHT) trial as well as data from non-interventional studies, literature, and post-marketing safety reports.

Regarding the efficacy, despite the more modest treatment differences between Mysimba and placebo observed in the post hoc analysis of the pivotal phase 3 studies compared with the original analyses, the weight change from baseline, as well as the ≥5% and ≥10% weight loss responder analyses, were all in favour of Mysimba. The results indicated a statistically significant reduction of body weight compared to placebo after approximately 1 year of treatment. In comparison, the treatment effect at week 52 in the ITT analysis of the NB-CVOT-1 study was somewhat lower compared to the results of the pivotal phase 3 trials. However, in this study, compared to placebo, the proportion of subjects with ≥5% weight loss from baseline and the proportion of subjects with ≥10% weight loss from baseline was declining beyond 1 year. Still, the results do not question the effect observed in the phase 3 studies leading to the authorisation of Mysimba and the conclusions that the efficacy of Mysimba in weight management is limited but considered to be clinically relevant. Beyond 1 year of treatment with Mysimba, limited clinical data are available. In the NB-CVOT-1 study, the mean differences in weight loss in the PP population at 52, 104, and 208 weeks were -3.66 kg (95% CI [-4.15, -3.17]), -3.16 kg (95% CI [-3.82, -2.49]), and -3.03 kg (95% CI [-3.87, -2.19]), respectively. However, for the ITT population, using an appropriate imputation method (reference-based multiple Imputation or BOCF), these values are expected to be lower. The CHMP further noted that the results from the NB-CVOT-1 study should be interpreted with caution due to its early termination. This may have impacted the robustness and reliability of the findings. In addition, this study was not designed to assess long-term efficacy on the reduction in body weight as either a primary or secondary endpoint.

Regarding safety, the reviewed pooled data of the phase 3 studies confirmed the safety outcomes reported in the marketing authorisation application for Mysimba. In these analyses, Mysimba was associated with less pronounced reductions in BP and heart rate compared to placebo. Over 1 year, the HR point estimates for MACE in the NB-CVOT-1 study suggested a trend towards a reduced risk for MACE, but the extent of this reduction decreased over time (HR 0.61, 95% CI, [0.2-1.29], 0.62, 95% CI, [0.39-0.98] and 0.73, 95% CI [0.47-1.14]) at ≤16 weeks, 16-52 weeks, and 52-104 weeks, respectively). In addition, the differences observed between the placebo and active treatment groups in this study for BP and heart rate were minimal. However, the information for patients receiving treatment beyond 1 year of treatment in this study was very scarce due to the high number of treatment discontinuations.

Additional data from non-interventional studies, literature and post-marketing reports do not add a concern in relation to the CV risk. The completed health outcomes analysis identified no evidence of excess CV risk and no statistically significant difference in MACE between Mysimba and the comparator group (lorcaserin). In another real-world study, the DUS NB-451, CV event were not common in patients receiving Mysimba. From the literature review and published meta-analysis, it seemed that Mysimba does not appear to significantly increase the risk of major CV events compared to other treatments. Further, the rate of events gathered from post-marketing safety reports did not raise a significant concern with the CV safety of Mysimba. The CHMP however noted that, while reassuring, this type of data brings limited value due to its inherent limitations. Consequently, it cannot alleviate the uncertainty related to long-term CV safety of Mysimba.

Hence, the CHMP considers that the CV safety concern, which was raised because of findings of unfavourable BP changes and increased heart rate at time of the marketing authorisation of Mysimba,

remains. Additionally, the data reviewed do not allow CHMP to conclude on the long-term CV safety of Mysimba and the uncertainty identified at the time of the marketing authorisation remains. Therefore, the uncertainties regarding long-term CV safety beyond 1 year of treatment still need to be addressed with data coming from a CVOT, as per the condition to the marketing authorisation.

In order to comply with the condition to the marketing authorisation and address the uncertainties in relation to the long-term CV risk, the MAH should submit the results of the NB-CVOT-3 (INFORMUS) study. The study is ongoing, and as of 31 January 2025, 2,825 patients had been randomised. The CHMP considered the study acceptable, with some protocol amendments, as a replacement of the CVOT study currently imposed as a condition to the marketing authorisation (category 1 study). The following amendments were introduced in the protocol: inclusion of an expanded MACE endpoint as a new secondary endpoint (i.e., MACE or any coronary, cerebrovascular and peripheral revascularization events, or hospitalization for heart failure), other additional endpoints (all-cause death and time to all-cause death), sensitivity analyses to mitigate potential misclassification of events, additional analysis to address competing risks, as well as new analyses to strengthen the understanding of the treatment effect under various scenarios (e.g. different intercurrent event strategies for treatment discontinuation and death, informative censoring due to loss of follow-up and different analysis priors). The study results should be submitted by 31 December 2028. Additionally, the MAH should submit annual reports on the study progress. This is to be reflected in the risk management plan (RMP) accordingly.

To note, while the Bayesian approach to be followed in the study was accepted, the CHMP considers that the frequentist approach is of equally importance and should lead to similar conclusions. In addition, sensitivity analyses using weakly and non-informative priors are essential to contextualise the study results and should be provided by the MAH with the study results. Therefore, if not provided by the MAH, these analyses and simulations concerning the frequentist operating characteristics for the Bayesian analyses will be requested when the study results are available.

Importantly, the CHMP emphasised that the study results will not be evaluated simply based on its primary non-inferiority test. The magnitude and precision of the risk estimates in the study will be assessed against the totality of data generated in the study and in the context of all available evidence on the CV safety of Mysimba. Remaining uncertainty in the study results, related to poor precision of estimated risks, insufficient follow-up, or concerns regarding remaining bias, will be considered in the overall assessment and may adversely impact the benefit-risk balance of Mysimba.

Further, while the NB-CVOT-3 study results are not available and the uncertainty regarding the long-term CV risk remains, the CHMP considered that only patients who benefit from long-term treatment should continue treatment with Mysimba for longer than 1 year, considering the potential long-term CV risk of Mysimba. As a consequence, the CHMP recommends that treatment with Mysimba beyond 1 year should be discontinued if the efficacy success criteria already established for the product after 16 weeks of treatment is not at least maintained. Namely, treatment with Mysimba should be discontinued if patients, after one year of treatment, have not maintained a loss of at least 5% of their body weight. Additionally, it should be specified in the product information that the CV risks of Mysimba when given for longer than a year have not been fully determined. Further, when annually assessing the treatment continuation, HCPs should monitor the absence of adverse change in patients' CV risk and maintenance of weight loss of at least 5% of their initial weight. This assessment should be conducted in discussion with the patient (summary of product characteristics [SmPC] section 4.2). With these measures, only patients sustainably benefiting from treatment will be exposed to Mysimba for more than 1 year, thereby minimising potential long-term CV risks for those who do not benefit from it. In order to adequately inform HCPs of these measures and ensure appropriate use of Mysimba, the existent prescriber guide (named 'physician prescribing checklist') should be updated to reflect this

recommendation. A direct healthcare professional communication (DHPC) is also to be distributed. Additionally, the available educational materials to be used by HCPs when discussing the treatment with patients should be reflected in the product information (SmPC section 4.4).

In view of the above, the Committee considers that the benefit-risk balance of Mysimba remains favourable subject to the agreed condition to the marketing authorisation, and taking into account the agreed amendments to the product information and other risk minimisation measures.

4. Summary of new activities and measures

4.1. Risk management

The MAH should operate a risk management system described in a RMP which has been endorsed as part of the current review. The CHMP considered that the following should be added regarding the existing important identified risk 'increases in blood pressure or heart rate':

1. Amendments to the product information and prescriber guide ('physician prescribing checklist').
2. Implementation of a DHPC.
3. Update of the additional pharmacovigilance activities, including details on the newly accepted NB-CVOT-3 (INFORMUS) study as a category 1 post-authorisation safety study (PASS) replacing the previous CVOT study.

4.1.1. Risk minimisation measures

4.1.1.1. Routine risk minimisation measures

Amendments to the product information

The CHMP considered that amendments to sections 4.2 and 4.4 of the SmPC were necessary to reflect the outcome of this review.

Section 4.2 should be updated to include information about the undetermined long-term CV risks of Mysimba. In addition, this section should indicate that Mysimba is to be discontinued after one year if a patient has not maintained a loss of at least 5% of their initial body weight. Further, the section should reflect further details on the annual assessment to be conducted by HCPs in discussion with the patients. When annually assessing the treatment continuation, HCPs should monitor the absence of adverse change in patients' CV risk and maintenance of weight loss of at least 5% of their initial weight. This assessment should be conducted in discussion with the patient.

Section 4.4 should provide a list of the available educational materials to be used by HCPs when discussing treatment with patients.

The package leaflet is amended accordingly.

4.1.1.2. Additional risk minimisation measures

The key elements in the existing prescriber guide ('physician prescribing checklist') are to be updated to include the need to discontinue treatment with Mysimba following annual assessment if patients have not maintained a loss of at least the 5% of their initial body weight.

4.1.2. Pharmacovigilance activities

4.1.2.1. Additional pharmacovigilance activities

The MAH shall conduct and submit the results of a phase 4, prospective, randomised, double-blind, placebo-controlled study CVOT-3 – INFORMUS, in accordance with the agreed protocol. The final clinical study report is to be submitted by 31 December 2028 (see also section 5.).

This study replaces the previously imposed condition to the marketing authorisation and is reflected as category 1 in the RMP. Annual progress reports shall be submitted to the EMA starting one year after the CHMP opinion date and annually thereafter. The first annual progress report, including the DMC charter outlining the setup and conduct of the planned DMC data analyses, will be submitted one year after adoption of the CHMP opinion on the present procedure. Additionally, the annual reports should discuss the rate of enrolment to ensure a timely completion of study. Further, the number of randomised patients, number and proportion of patients permanently discontinuing treatment, and number and proportion of participants who withdrew consent or were lost to follow-up should also be provided.

4.2. Direct healthcare professional communications and communication plan

The Committee adopted the wording of a DHPC to inform HCP about the undetermined long-term CV risk and new recommendations on annual assessment. The Committee also agreed on a communication plan.

5. Condition(s) to the marketing authorisation

The MAH shall complete the below condition, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

Interventional post-authorisation safety study (PASS): In order to further characterise the long-term cardiovascular safety, including the occurrence of major adverse cardiovascular events (MACE) related to naltrexone hydrochloride extended release (ER) and bupropion hydrochloride ER combination in the treatment of patients with obesity or who are overweight, the MAH should submit the results of the prospective, randomised, double-blind, placebo-controlled study CVOT-3 – INFORMUS.	The final study report should be submitted by: 31 December 2028

6. Grounds for opinion

Whereas,

- The CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Mysimba.
- The CHMP reviewed all available data submitted by the MAH in relation to the long-term cardiovascular safety and the efficacy of Mysimba in its authorised indication. This included data from the pivotal clinical trials, additional post hoc analysis, data from the early-terminated NB-CVOT-1 trial as well as data from non-interventional studies, literature and post-marketing

safety reports. In addition, the CHMP considered a new CVOT study protocol, proposed by the MAH in order to further characterise the long-term cardiovascular safety and to fulfil the Annex II.D condition to the marketing authorisation.

- The CHMP considers that the available data remain insufficient to address the concern already identified at the time of the marketing authorisation regarding the long-term cardiovascular safety.
- While this uncertainty remains, the CHMP considers that treatment with Mysimba should be discontinued after one year if a patient has not maintained a loss of at least 5% of their initial body weight. Further, when annually assessing the treatment continuation, healthcare professionals should monitor the absence of adverse change in patients' cardiovascular risk and maintenance of weight loss of at least 5% of their initial weight. This assessment should be conducted in discussion with the patient.
- Finally, the CHMP considers that the ongoing cardiovascular safety study (INFORMUS), as per its further amended protocol, is appropriate to generate evidence on the long-term cardiovascular safety of Mysimba. Additional relevant analyses not reflected in the protocol will be requested when the study results are available, if necessary. Overall, the study is considered acceptable as replacement of the CVOT study that is currently imposed as a condition to the marketing authorisation.

In view of the above, the CHMP concludes that the benefit-risk balance of Mysimba remains favourable subject to the agreed condition to the marketing authorisation, and taking into account the implementation of the agreed amendments to the product information and the other risk minimisation measures.

The CHMP, as a consequence, recommends a variation to the terms of the marketing authorisation for Mysimba.

References

Aalen O.O., Johansen S., 'An empirical transition matrix for nonhomogeneous Markov chains based on censored observations', Scand J Stat, Vol. 5(2), 1978, p. 141-150.

Alsuhibani A., Alrasheed M., Gari M., Hincapie A.L., Guo J.J., 'Descriptive analysis of reported adverse events associated with anti-obesity medications using FDA Adverse Event Reporting System (FAERS) databases 2013-2020', Int J Clin Pharm, Vol. 44(1), 2022, p.172-179.

Apovian C.M., Aronne L., Rubino D., Still C., Wyatt H., Burns C., et al, 'A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II)', Obesity (Silver Spring), Vol. 21(5), 2013, p. 935-43.

Calderon G., Gonzalez-Izundegui D., Shan L., Garcia-Valencia O.A., Cifuentes L., Campos A., et al., 'Effectiveness of anti-obesity medications approved for long-term use in a multidisciplinary weight management program: a multicenter clinical experience', Int J Obes (Lond), Vol. 46(3), 2022, p. 555-563.

Dahlberg S., Chang E.T., Weiss S.R., Dopart P., Gould E., Ritchey M.E., 'Use of contrave, naltrexone with bupropion, bupropion, or naltrexone and major adverse cardiovascular events: a systematic literature review', Diabetes Metab Syndr Obes, Vol.15, 2022, p. 3049-67.

Dong Z., Xu L., Liu H., Lv Y., Zheng Q, Li L., 'Comparative efficacy of five long-term weight loss drugs: quantitative information for medication guidelines', Obes Rev, Vol. 18(12), December 2017, p. 1377-1385.

Dutta N., Tessier K., Langer J., Harindhanavudhi T., Sibley S., Billington C., et al., 'Health outcomes in patients with obesity and type 2 diabetes undergoing medical weight management. Obesity', Obesity (Silver Spring), Poster Abstracts, Vol. 30 Supplement 1 (267), 2022, p. 30:55-293.

Gorelik E., Gorelik B., Masarwa R., Perlman A., Hirsh-Raccah B., Matok I., 'The cardiovascular safety of antiobesity drugs-analysis of signals in the FDA Adverse Event Report System Database', Int J Obes, Vol. 44(5), 2020, p. 1021-1027.

Halseth A., Burns C.M., Walsh B., Klassen P., Kolotkin R.L., 'Combination prolonged-release naltrexone/bupropion therapy resulted in clinically meaningful improvements in weight and quality of life (QOL)-integrated analysis of four phase 3 trials', Obesity Facts, Vol. 8(S1), 2015, p. 238239.

Iannone A., Natale P., Palmer S.C., Nicolucci A., Rendina M., Giorgino F., et al., 'Clinical outcomes associated with drugs for obesity and overweight: A systematic review and network meta-analysis of randomized controlled trials', Diabetes Obes Metab, Vol. 25(9), 2023, p. 2535-2544.

Nissen S.E., Wolski K.E., Prcela L., Wadden T., Buse J.B., Bakris G., et al., 'Effect of naltrexone-bupropion on MACEs in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial', JAMA, Vol. 315(10), 2016, p. 990-1004.

Onakpoya I.J., Lee J.J., Mahtani K.R., Aronson J.K., Heneghan C.J., 'Naltrexone-bupropion (Mysimba) in management of obesity: A systematic review and meta-analysis of unpublished clinical study reports', Br J Clin Pharmacol, Vol 86(4), 2020, p. 646-667.

Sposito A.C., Bonilha I., Luchiari B., Benchimol A., Hohl A., Moura F., Cercato C., Geloneze B., Nadruz W., Aguilar-Salinas C., Carvalho L.S.F., 'Cardiovascular safety of naltrexone and bupropion therapy: Systematic review and meta-analyses', Obes Rev, Vol 22(6), 2021, p. e13224.

Zhao Y., Herring A.H., Zhou H., Ali M.W., Koch G.G., 'A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring', J Biopharm Stat, Vol. 24(2), 2014, p.229-253.

Appendix 1

Divergent position

Article 20 of Regulation (EC) No 726/2004

Procedure No: EMEA/H/A-20/1530/C/3687/0065

Mysimba (INN: naltrexone /bupropion)

Divergent statement

The undersigned CHMP member does not agree with the CHMP positive opinion proposing to maintain a benefit/risk balance positive of Mysimba (naltrexone, bupropion) in the management of weight in adult patients following the referral procedure EMEA/H/C/003687/A20/0065, mainly based on limited efficacy demonstration in weight management and strong safety uncertainties regarding cardiovascular safety and poor tolerability.

The proposed risk minimization measures are not believed to mitigate the above mentioned safety concerns.

CHMP member(s) expressing a divergent opinion:

- Alexandre Moreau (France)