Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions
Taking into account the PRAC Assessment Report on the PSUR(s) for bupropion, the scientific conclusions are as follows:

In view of available data on the risk of toxic epidermal necrolysis (TEN) from post-marketing case reports including two strong, probable cases from literature and some possible cases-and considering that the underlying pathophysiology of TEN is similar as that of Stevens-Johnson Syndrome (SJS) which is already a listed adverse reaction for bupropion, the PRAC considers that a causal relationship between bupropion and TEN is at least a reasonable possibility. The PRAC concluded that the product information of products containing bupropion should be accordingly amended.

In view of available data on the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) from the literature and spontaneous reports, including a positive de-challenge in one strong literature case, and a plausible underlying mechanism, the PRAC considers that a causal relationship between bupropion and DRESS is at least a reasonable possibility. The PRAC concluded that the product information of products containing bupropion should be accordingly amended.

Considering the data on TEN and DRESS that became available in current PSUSA, and the Severe cutaneous adverse reactions (SCARs) already labelled as ADRs for bupropion (Stevens-Johnson Syndrome (SJS), Acute generalized exanthematous pustulosis (AGEP)), the PRAC concluded that it is necessary to implement a separate warning for SCARs in SmPC section 4.4 of bupropion containing products. All SCARs currently listed in SmPC section 4.8 as well as the SCARs added as new ADRs in current PSUSA should be reflected in the warning so that the warning covers all SCARs that have been reported with bupropion. Consequently, SJS should be removed from the current warning on hypersensitivity. Symptoms of SCARs and actions to be taken by patients need to be reflected in a comprehensive wording (addressing safety information and actions to take) to be included in Package leaflet section 4. This to ensure that both health care professionals and patients are well informed about and warned for these serious skin reactions that may be life threatening for patients.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for bupropion the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing bupropion is unchanged subject to the proposed changes to the product information.

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

*The current warning on hypersensitivity should be amended by removing Stevens-Johnson syndrome as follows (new text **underlined and in bold;** deleted text ~~strike through~~):*

Hypersensitivity

<Product name> should be discontinued promptly if patients experience hypersensitivity reactions during treatment. Clinicians should be aware that symptoms may progress or recur following the discontinuation of <product name> and should ensure symptomatic treatment is administered for an adequate length of time (at least one week). Symptoms typically include skin rash, pruritus, urticaria or chest pain, but more severe reactions may include angioedema, dyspnoea/bronchospasm, anaphylactic shock, **and** erythema multiforme ~~or Stevens-Johnson syndrome~~. Arthralgia, myalgia and fever have also been reported in association with rash and other symptoms suggestive of delayed hypersensitivity (see section 4.8). These symptoms may resemble serum sickness (see section 4.8).* In most patients symptoms improved after stopping bupropion and initiating treatment with antihistamine or corticosteroids, and resolved over time.

Allergic reactions can last a long time. If your doctor prescribes something to help with allergic symptoms, make sure you finish the course.*

*Text that is highlighted in grey differs between SmPCs of bupropion containing products.

*The following separate SCAR warning should be added (new text **underlined and in bold**):*

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with bupropion treatment.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, bupropion should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS, TEN, AGEP, or DRESS with the use of bupropion, the treatment must not be restarted in this patient at any time.

- Section 4.8

*The following adverse reactions should be added under the SOC Skin and subcutaneous tissue disorders with a frequency not known (new text **underlined and in bold**):*

toxic epidermal necrolysis

drug reaction with eosinophilia and systemic symptoms

Package Leaflet

- Section 2

Serious skin reactions

Serious skin reactions, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in association with [Product name]. Stop using [Product name] and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

- Section 4

Symptoms of SJS should be removed from the current wording on allergic reactions (*deleted text ~~strike through~~)*:

Allergic reactions

Some people may get allergic reactions to <product name>. These include

• Red skin or rash (like nettle rash), ~~blisters or~~ **and** itchy lumps (hives) on the skin. ~~Some skin rashes may need hospital treatment, especially if you also have a sore mouth or sore eyes.~~

• Unusual wheezing or difficulty in breathing

• Swollen eyelids, lips or tongue

• Pains in muscles or joints

• Collapse or blackout.

OR

Rarely (up to 1 in 1000) people may have potentially serious allergic reactions to <product name>. Signs of allergic reactions include:

• skin rash (including itchy, bumpy rash). ~~Some skin rashes may need hospital treatment, especially if you also have a sore mouth or sore eyes~~

• Unusual wheezing or difficulty in breathing

• Swollen eyelids, lips or tongue

• Pains in muscles or joints

• Collapse or blackout.

➔ **If you have any signs of an allergic reaction** contact a doctor at once. **Don't take any more tablets.**

Allergic reactions can last a long time. If your doctor prescribes something to help with allergic symptoms, make sure you finish the course.*

*Text that is highlighted in grey is not included in all SmPCs of bupropion containing products.

*SCARs as serious adverse reactions should be warned for as follows (new text **underlined and in bold**; deleted text ~~strike through~~):*

Serious skin reactions

Stop using bupropion and seek medical attention immediately if you notice any of the following symptoms:

- **<Frequency as per current SmPC (*either rare or very rare*)>*: Reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome).**
- **Frequency not known: Large areas of blistering and extensive skin peeling occur in a severe form of above described ~~this~~ serious skin reaction (toxic epidermal necrolysis).**
- **Frequency not known: Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome). The onset of this syndrome is usually delayed (2-6 weeks after treatment initiation).**
- **Frequency not known: A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis).**

*Frequency of occurrence of SJS differs between SmPCs of bupropion containing products. The currently listed frequency should be maintained in the updated Product information.

Any currently included safety information about AGEP should be removed from section 4.

Also SJS as other side effect (i.e. "Severe skin rashes that may affect the mouth and other parts of the body and can be life-threatening") should be removed from section 4.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	2 November 2025
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	1 January 2026