CBG MEB

Type II variation

Public Assessment Report

Desuric, tablets 100 mg (benzbromarone)

Marketing Authorisation Holder: ProStrakan Ltd

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation or variation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and care takers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

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To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

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I. RECOMMENDATION

Based on the review of the data provided, the Medicines Evaluation Board of the Netherlands (MEB) considers that the variation for Desuric, tablets 100 mg (benzbromarone), for the proposed change in wording of the indication is approvable.

The extension of the indication is underlined:

Desuric is indicated for the treatment of gout in adult patients with allopurinol hypersensitivity, who have contra-indications regarding first line treatment option allopurinol, in whom allopurinol is not effective or who have unacceptable side effects of allopurinol.

II. EXECUTIVE SUMMARY

Introduction
Desuric 100 mg tablets have been registered in the Netherlands since 19 April 1972 for the broad indication gout. The product contains the active substance benzbromarone, a well-known anti-gout uricosuric drug, which stimulates urinary excretion of urate. In 2003 the indication was restricted because of reports of serious hepatic adverse events. The Board was of the opinion that the registration should be continued as there was a need for treatment in some patients where allopurinol would not be a therapeutic option. The restriction in the wording of the indication was introduced for safety reasons. (See also: http://www.cbg-meb.nl/CBG/en/human-medicines/actueel/2003-10-29-Desuric+available+for+limited+indications/default.htm).

Scope of the variation
This application concerns a type II variation to update the wording of the indication. Because of the risk of drug-induced liver injury (DILI), the indication of benzbromarone is restricted to a second line treatment option, in patients who have contra-indications regarding the first line treatment option allopurinol, or allopurinol hypersensitivity. With this variation the Marketing Authorisation Holder (MAH) proposed to extend the indication to patients in whom allopurinol is not effective or who have unacceptable side effects of allopurinol.

III. SCIENTIFIC DISCUSSION

Clinical aspects
The MEB evaluated whether an extension of the indication to include patients failing or intolerant to allopurinol is sufficiently justified.

Failure to allopurinol is common. As benzbromarone has a different mode of action than the xanthine oxidase inhibitor (XOI) allopurinol, it may serve as an alternative treatment option. There is evidence from a small-scale randomised study in a Dutch primary care setting, with data of 55 patients analysed, that benzbromarone is indeed effective in patients irresponsive to allopurinol, more than probenicid (responder rate 92% vs. 65%) (Reinders et al 2009[1]). Moreover, according to a recent meta-analysis, benzbromarone is a more potent drug (75% more effective in reducing serum urate levels than allopurinol at regular doses).

In addition, there are limited alternative treatment options for patients failing or intolerant to allopurinol available. Febuxostat is another, more powerful XOI compared to allopurinol, but it has not been shown whether febuxostat is effective in the second line treatment setting. The alternative uricosuric drug probenecid is no longer registered in the Netherlands. Recently, Krystexxa, a pegylated uricase, was accepted by the CHMP, but only for end-stage patients with tophi in a hospital setting, because of the high risk of immunogenicity and/or infusion reactions.

[1] Reinders MK, Van Roon EN, Jansen TLThA, et al. *Efficacy and tolerability of urate lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol*. Ann Rheum Dis. 2009;68(1):51–56.

It has been estimated that the risk of hepatotoxicity is 1:17 000. The MAH argued that it is not expected that the new indication will significantly increase the use of benzbromarone - and thus the incidence of DILI. Moreover, benzbromarone is already used for the newly proposed target group, align with the applicable guidelines for the treatment of gout.

The MAH proposed to extend the monitoring period of liver enzymes up to 6 months as included in section 4.4 of the SmPC to monitoring throughout the whole treatment period. As it is understood from the literature that DILI of benzbromarone can be considered idiosyncratic, and may occur anytime, not only in the first months, this more extensive period of liver enzyme monitoring is supported.

Hepatic injury from benzbromarone usually arises as a hepatocellular pattern of enzyme elevations, therefore ALAT and ASAT monitoring would be appropriate. However, since other forms of liver injury are possible as well, it is proposed that other liver function tests are also included in the periodic monitoring (alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT)). The proposed laboratory tests including both signals of hepatocellular injury and cholestasis are considered relevant in detecting DILI and are therefore accepted.

There are no recommendations for the frequency of liver function monitoring during use of drugs which can cause idiosyncratic liver reactions, neither in literature, nor in guidelines from Health Authorities. The MAH proposed 3 monthly testing of the specified liver function tests during the use of benzbromarone. This requirement for a 3 months' monitoring interval is however considered rather arbitrary, and is not justified based on data. The recommendation should therefore read that liver function (alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT)) must be tested before treatment is initiated and should be monitored at regular intervals during treatment.

There is a statement in the SmPC (which is also reflected in the package leaflet) informing patients of the symptoms and signs of hepatoxicity and the need to report them immediately to the physician. This would further ensure early discontinuation of benzbromarone if DILI occurs.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The Board concluded that the proposed extension of the therapeutic indication to include patients in whom allopurinol is not effective or who have unacceptable side effects of allopurinol, is justified. There is sufficient evidence that benzbromarone is effective in patients irresponsive to allopurinol, and there are limited treatment options available for the second line. The appropriate monitoring instructions regarding liver function were discussed and determined as given below. Overall, considering the justifications provided and in view of the Dutch treatment guidelines, the MEB came to a positive conclusion. This variation application was approved on 2 April 2014.

V. CHANGES IN PRODUCT INFORMATION

Major changes to the product information in the context of this variation are given below, in Dutch. Added text is underlined, strike-through text was deleted.

SmPC

Rubriek 4.1 - Therapeutische indicaties
Desuric is bestemd voor de behandeling van jicht alleen bij volwassen patiënten die allergisch zijn voor allopurinol of bij wie er een contra-indicatie is voor allopurinol, of bij wie allopurinol onvoldoende resultaat of onaanvaardbare bijwerkingen geeft.

Rubriek 4.4 - Speciale waarschuwingen en voorzorgen bij gebruik
Er zijn enkele gevallen van leverbeschadiging met fatale afloop tijdens behandeling met benzbromaron gemeld. Voor de start van de behandeling dient de leverfunctie getest te worden (~~inclusief transaminase bepaling~~ ten minste: alanine-aminotransferase [ALAT], aspartaatamino-transferase [ASAT], alkalische fosfatase, totaal bilirubine en gammaglutamyltransferase [gamma-

GT]). Vervolgens dienen deze testen gedurende ~~tenminste de eerste zes maanden van~~ de behandeling periodiek uitgevoerd te worden ~~(zie rubriek 4.3)~~. De behandeling dient onmiddellijk en definitief gestopt te worden indien de leverfunctie ~~transaminase~~ waarden boven de normale bovengrens zijn. Daarna moet de patiënt onder strikt toezicht blijven totdat de leverfunctietesten weer normaal zijn.

Rubriek 4.5 - Interacties met andere geneesmiddelen en andere vormen van interactie
Systemisch beschikbaar benzbromaron wordt gemetaboliseerd via CYP2C9 in de lever. Gelijktijdig gebruik van geneesmiddelen (inclusief kruidengeneesmiddelen) waarvan bekend is dat zij CYP2C9 remmen, kunnen het metabolisme van benzbromaron beïnvloeden en daardoor bloedconcentraties van benzbromaron verhogen.

Benzbromaron is een remmer van CYP2C9 in de lever daarom kan bij gelijktijdige toediening van andere door CYP2C9 gemetaboliseerde geneesmiddelen het metabolisme van deze geneesmiddelen verminderen. In een studie is aangetoond dat het metabolisme van warfarine werd geremd door gelijktijdig gebruik van benzbromaron. Daarom kan het nodig zijn de dosis warfarine te verlagen.

Bijsluiter

Rubriek 1 - Waarvoor wordt Desuric gebruikt?
Desuric is bestemd voor de behandeling van jicht alleen bij volwassen patiënten die allergisch zijn voor allopurinol (een ander anti-jichtmiddel) of die allopurinol niet mogen gebruiken, of bij wie allopurinol onvoldoende resultaat of onaanvaardbare bijwerkingen geeft.

Rubriek 2 - Wanneer moet u extra voorzichtig zijn met dit middel?
Er zijn enkele gevallen van ernstige leverbeschadiging tijdens behandeling met Desuric gemeld, soms met fatale afloop. Deze leverbeschadiging treedt meestal gedurende de eerste maanden van de behandeling op.

Daarom zal de arts uw leverfunctie voor de start van de behandeling testen. Daarna zullen deze testen ~~gedurende tenminste de eerste zesde maanden~~ herhaaldelijk worden uitgevoerd.

U dient onmiddellijk uw arts te waarschuwen indien u misselijk bent, moet overgeven, buikpijn, algemene spierzwakte of geelzucht heeft.